(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
27 December 2002 (27.12.2002)

PCT

(10) International Publication Number
WO 02/102297 A2

(51) International Patent Classification[7]: A61K

(21) International Application Number: PCT/EP02/06013

(22) International Filing Date: 31 May 2002 (31.05.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
101 29 320.8 19 June 2001 (19.06.2001) DE
60/364,904 14 March 2002 (14.03.2002) US

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(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *without international search report and to be republished upon receipt of that report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 02/102297 A2

(54) Title: USE OF COX-2 INHIBITORS FOR THE TREATMENT OF SCHIZOPHRENIA, DELUSIONAL DISORDERS, AFFECTIVE DISORDERS, AUTISM OR TIC DISORDERS

(57) Abstract: The invention concerns the use of a COX-2 inhibitor for the treatment of psychiatric disorders such as schizophrenia, delusional disorders, affective disorders, autism or tic disorders, in particular chronic schizophrenic psychoses and schizoaffective psychoses, temporary acute psychotic disorders, depressive episodes, recurring depressive episodes, manic episodes and bipolar affective disorders. Moreover, the invention is concerned with the use of a COX-2 inhibitor, in particular celecoxib, in combination with a neuroleptic drug, in particular risperidone, or an antidepressant, for the treatment of psychiatric disorders such as schizophrenia, delusional disorders, affective disorders, autism or tic disorders.

Use of COX-2 Inhibitors for the Treatment of Schizophrenia, Delusional Disorders, Affective Disorders, Autism or Tic Disorders

The invention concerns the use of a COX-2 (cyclooxygenase-2) inhibitor for the treatment of psychiatric disorders such as schizophrenia, delusional disorders, affective disorders, autism or tic disorders, in particular chronic schizophrenic psychoses and schizoaffective psychoses, temporary acute psychotic disorders, depressive episodes, recurring depressive episodes, manic episodes and bipolar affective disorders.

Moreover, the invention is concerned with the use of a COX-2 inhibitor in combination with a neuroleptic drug or an antidepressant for the treatment of psychiatric disorders such as schizophrenia, delusional disorders, affective disorders, autism or tic disorders.

A relation between immunological dysfunctions and psychotic diseases, such as schizophrenia or affective disorders, has been discussed controversially over the last century.

In the case of schizophrenia for instance the pathogenesis is still unknown, but many findings indicate that schizophrenia is a syndrome based on different pathogenetic processes.

An inflammatory/immunological pathogenesis has been discussed for a subgroup of schizophrenic patients (Yolken RH, Torrey EF: Viruses, schizophrenia, and bipolar disorder. Clin Microbiol Rev 1995; 8:131-145; Körschenhausen D, Hampel H, Ackenheil M, Penning R, Müller N: Fibrin degradation products in post mortem brain tissue of schizophrenics: a possible marker for underlying inflammatory processes, Schizophr Res 1996; 19: 103-109; Müller N, Ackenheil M: Psychoneuroimmunology

and the cytokine-network in the CNS: implications for psychiatric disorders. Prog Neuropsychopharmacol & Biol Psychiat 1998; 22: 1-33). Studies showed that activating cytokines like interleukin-1 (IL-1) and IL-2 are increased in the cerebrospinal fluid of schizophrenic patients compared to controls (Sirota P, Schild K, Elizur A, Djaldetti M, Fishman P: Increased Interleukin-1 and Interleukin-3 like activity in schizophrenic patients. Prog Neuropsychopharmacol & Biol Psychiatry 1995; 19: 85-83; Licinio J, Seibyl, JP, Altemus M, Charney DS, Krystal JH: Elevated levels of Interleukin-2 in neuroleptic-free schizophrenics. Am J Psychiatry 1993; 150: 1408-1410), and that high levels of IL-2 in the cerebrospinal fluid are a predictor for the increased probability of a schizophrenic relapse (McAllister CG, van Kamen DP, Rehn TJ, Miller AL, Gurklis J, Kelley ME, Yao J, Peters JL: Increases in CSF levels of Interleukin-2 in schizophrenia: effects of recurrence of psychosis and medication status. Am J Psychiatry 1995; 152: 1291-1297).

On the other hand, in a subgroup of schizophrenic patients a decreased immune response compared to controls has been observed, possibly due to a disturbance of antigen-presentation or antigen-recognition (Schwarz MJ, Riedel M, Ackenheil M, Müller N: Decreased levels of soluble intercellular adhesion molecule –1 (sICAM-1) in unmedicated and medicated schizophrenic patients. Biol Psychiatry 2000; 47: 29-33), e.g. the increased immune reaction in the central nervous system may not be adequately regulated by an immune reaction in the peripheral immune system. This was observed mostly in acute schizophrenic patients presenting a recent onset of the disorder.

Another group of schizophrenic patients, however, seems to present an over-activation of the peripheral immune system in the sense of autoimmune processes (Radaport MH, Müller N: Immunological states associated with schizophrenia. In: Ader R, Felten DL, Cohen N (eds) Psychoneuroimmunology, Third Edition. Vol. 2, San Diego, Academic Press, 2001; pp 373-382; Radaport MH, McAllister CG, Kim YS, Han JH, Pickar D, Nelson DM, Kirch DG, Paul SM: Increased soluble Interleukin-2 receptors in Caucasian and korean schizophrenic patients. Biol Psychiatry 1994; 35: 767-771). In several studies, increased titers of antibodies against the heat-shock-protein 60 were observed (Kilidireas K, Latov N, Strauss DH,

Aviva DG, Hashim GA, Gorman JM, Sadiq SA: Antibodies to human 60 KD hear-shock protein in patients with schizophrenia. Lancet 1992; 340: 569-572), the increase being accompanied by increased soluble IL-2 receptors in the serum and increased titers of the soluble adhesion molecule sICAM-1 (Radaport MH, Müller N: Immunological states associated with schizophrenia. In: Ader R, Felten DL, Cohen N (eds) Psychoneuroimmunology, Third Edition. Vol. 2, San Diego, Academic Press, 2001; pp 373-382; Schwarz MJ, Riedel M, Gruber R, Ackenheil M, Müller N: Antibodies to heat-shock proteins in schizophrenic patients – Implications for disease mechanism. Am J Psychiatry 1999; 156, 1103,1104). The close relationship between high sVCAM-1 titers and more pronounced schizophrenic negative symptoms (Schwarz MJ, Riedel M, Gruber R, Ackenheil M, Müller N: Levels of soluble adhesion molecules in schizophrenia: Relation to psychopathology. In: N. Müller (Hrg) Psychiatry, Psychoneuroimmunology, and Viruses. Springer Verlag Wien, 1999; NY, pp. 121-130) as well as between high IgG levels in the cerebrospinal fluid and more pronounced negative symptoms further support this observation (Müller N, Ackenheil M: Immunoglobulin and albumin contents of cerebrospinal fluid in schizophrenic patients: The relationship to negative sympomatology. Schizophrenia Res 1995; 14: 223-228).

Affective diseases, in particular depressive diseases, may also have an inflammatory genesis. This is manifested in the fact that general inflammatory diseases are accompanied by depressive syndromes to an increased extent as well as in the fact that in depressive diseases, signs of inflammation occur more frequently in comparison to psychologically healthy persons. Scientifically, this was expressed in the monocyte/macrophage hypothesis of depression.

The occurrence of tics as well as of autism has also been discussed in many cases as a consequence of inflammatory processes.

The invention is based on the idea that substances with immunomodulatory properties could be used for the treatment of psychiatric disorders such as schizophrenia, delusional disorders, affective disorders, autism or tic disorders, which are at least partially based on immunological pathogenetic processes.

For example, in the treatment of schizophrenia, a number of neuroleptic drugs (so-called classical and atypical neuroleptics) have become available, among which the more recent atypical neuroleptics excel by comparatively good effectiveness with a more favorable side effect profile. Unlike the classical neuroleptics, which are mainly effective for treating the positive symptoms of schizophrenia, the atypical neuroleptics improve both positive symptoms (hallucinations, delusions, and conceptual disorganization) and negative symptoms (apathy, social withdrawal, affective flattening, and poverty of speech) of schizophrenia. Plus, presumably due to their altered receptor binding profile, the atypicals cause minimal extrapyramidal symptoms and rarely cause tardive dyskinesias.
Anyhow, neuroleptics in general act as syndrome oriented therapy and less as a causal therapy.

Therefore, a need exists for further medicaments for the treatment of psychiatric disorders such as schizophrenia, delusional disorders, affective disorders, autism or tic disorders.

The present invention is directed to the use of COX-2 inhibitors for the manufacture of a medicament for the treatment of psychiatric disorders such as schizophrenia, delusional disorders, affective disorders, autism or tic disorders, in particular chronic schizophrenic psychosis and schizoaffective psychosis, temporary acute psychotic disorders, depressive episodes, recurring depressive episodes, manic episodes and bipolar affective disorders.
In the context of the present invention a treatment of a disease or disorder is meant to cover the actual therapy as well as maintenance therapy and prophylaxis against recurrence.

Furthermore, the invention concerns the use of COX-2 inhibitors in combination with neuroleptics or antidepressants for the treatment of psychiatric disorders such as schizophrenia, delusional disorders, affective disorders, autism or tic disorders, in particular chronic schizophrenic psychosis and schizoaffective psychosis, temporary acute psychotic disorders, depressive episodes, recurring depressive episodes,

manic episodes and bipolar affective disorders.

The invention is also directed to a novel kit-of-parts that is suitable for use in the treatment of psychiatric disorders such as schizophrenia, delusional disorders, affective disorders, autism or tic disorders, the kit comprising a first dosage form comprising a neuroleptic or an antidepressant and a second dosage form comprising a COX-2 inhibitor, for simultaneous, separate or sequential administration.

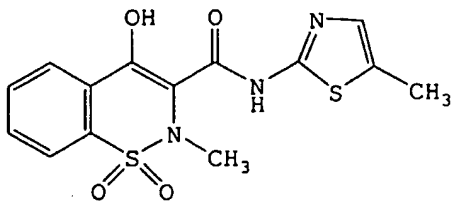
The COX-2 inhibitors of the present invention belong to the class of nonsteroidal anti-inflammatory drugs (NSAIDs). It has been known for some time that many of the common NSAIDs modulate prostaglandin synthesis by inhibition of cyclooxygenases that catalyze the transformation of arachidonic acid - the first step in the prostaglandin synthesis pathway. However, the use of high doses of many common NSAIDs can produce severe side effects that limit their therapeutic potential. In an effort to reduce the unwanted side effects of common NSAIDS, it was discovered that two cyclooxygenases are involved in the transformation of arachidonic acid as the first step in the prostaglandin synthesis pathway. These enzymes have been termed cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2)(Needleman, P. *et al., J. Rheumatol., 24, Suppl.49*:6 - 8 (1997);Fu, J. Y., *et al., J. Biol. Chem., 265(28)*:16737-40 (1990)). COX-1 has been shown to be a constitutively produced enzyme that is involved in many of the non-inflammatory regulatory functions associated with prostaglandins. COX-2, on the other hand, is an inducible enzyme having significant involvement in the inflammatory process. Inflammation causes the induction of COX-2, leading to the release of prostanoids, which sensitize peripheral nociceptor terminals and produce localized pain hypersensitivity (Samad, T. A. *et al., Nature, 410(6827)*:471-5 (2001)). Many of the common NSAIDs are now known to be inhibitors of both COX-1 and COX-2. Accordingly, when administered in sufficiently high levels, these NSAIDs affect not only the inflammatory consequences of COX-2 activity, but also the beneficial activities of COX-1. Recently, compounds that selectively inhibit COX-2 to a greater extent than the activity of COX-1 have been discovered. These new COX-2 inhibitors are believed to offer advantages that include the capacity to prevent or reduce inflammation while avoiding harmful side effects associated with the inhibition of COX-1, such as gastrointestinal and renal

side effects, as well as inhibition of thrombocyte aggregation.

The use of COX-2 inhibitors in the therapy of arthritis and related indications is known. US 5,760,068 describes the use of COX-2 inhibitors for the treatment of rheumatoid arthritis and osteoarthritis. WO 00/32189 discloses the preparation of pharmaceutical compositions containing the COX-2 inhibitor celecoxib and the use of celecoxib for the treatment of rheumatoid arthritis or as a painkiller.

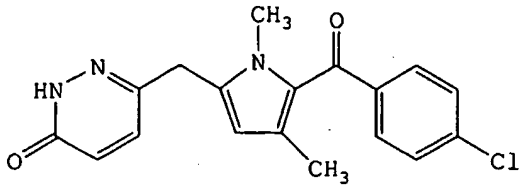
The term COX-2 inhibitor embraces compounds which selectively inhibit cyclooxygenase-2 over cyclooxygenase-1, and also includes pharmaceutically acceptable salts thereof. Also included within the scope of the present invention are compounds that act as prodrugs of cyclooxygenase-2-selective inhibitors. As used herein in reference to COX-2 inhibitors, the term "prodrug" refers to a chemical compound that can be converted into an active COX-2 inhibitor by metabolic or simple chemical processes within the body of the subject.

The COX-2 inhibitor of the present invention can be, for example, the COX-2 inhibitor meloxicam, Formula B-1 (CAS registry number 71125-38-7), or a pharmaceutically acceptable salt or prodrug thereof.



B-1

In another embodiment of the invention the COX-2 inhibitor can be the COX-2 inhibitor RS 57067, 6-[[5-(4-chlorobenzoyl)-1,4-dimethyl-1H-pyrrol-2-yl]methyl]-3(2H)-pyridazinone, Formula B-2 (CAS registry number 179382-91-3), or a pharmaceutically acceptable salt or prodrug thereof.

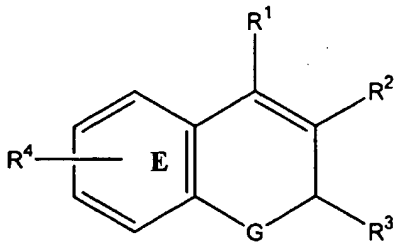


B-2

In a preferred embodiment of the invention the COX-2 inhibitor is a chromene derivative, that is a substituted benzopyran or a substituted benzopyran analog, and even more preferably selected from the group consisting of substituted benzothiopyrans, dihydroquinolines, or dihydronaphthalenes having the structure of any one of the compounds having a structure shown by general Formulas I, II, or III, shown below, and possessing, by way of example and not limitation, the structures disclosed in Table 1, including the diastereomers, enantiomers, racemates, tautomers, salts, esters, amides and prodrugs thereof.

Benzopyran COX-2 inhibitors useful in the practice of the present invention are described in U.S. Patent No. 6,034,256 and 6,077,850.

Formula I is:



I

wherein G is selected from the group consisting of O or S or NR^a;

wherein R^a is alkyl;

wherein R^1 is selected from the group consisting of H and aryl;

wherein R^2 is selected from the group consisting of carboxyl, aminocarbonyl,

alkylsulfonylaminocarbonyl and alkoxycarbonyl;

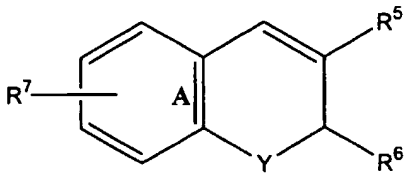
wherein R^3 is selected from the group consisting of haloalkyl, alkyl, aralkyl, cycloalkyl and aryl optionally substituted with one or more radicals selected from alkylthio, nitro and alkylsulfonyl; and

wherein R^4 is selected from the group consisting of one or more radicals selected from H, halo, alkyl, aralkyl, alkoxy, aryloxy, heteroaryloxy, aralkyloxy, heteroaralkyloxy, haloalkyl, haloalkoxy, alkylamino, arylamino, aralkylamino, heteroarylamino, heteroarylalkylamino, nitro, amino, aminosulfonyl, alkylaminosulfonyl, arylaminosulfonyl, heteroarylaminosulfonyl, aralkylaminosulfonyl, heteroaralkylaminosulfonyl, heterocyclosulfonyl, alkylsulfonyl, hydroxyarylcarbonyl, nitroaryl, optionally substituted aryl, optionally substituted heteroaryl, aralkylcarbonyl, heteroarylcarbonyl, arylcarbonyl, aminocarbonyl, and alkylcarbonyl;

or wherein R^4 together with ring E forms a naphthyl radical; or an isomer or pharmaceutically acceptable salt thereof; and

including the diastereomers, enantiomers, racemates, tautomers, salts, esters, amides and prodrugs thereof.

Formula II is:



II

wherein:

Y is selected from the group consisting of O or S or NR^b;

R^b is alkyl;

R^5 is selected from the group consisting of carboxyl, aminocarbonyl, alkylsulfonylaminocarbonyl and alkoxycarbonyl;

R^6 is selected from the group consisting of haloalkyl, alkyl, aralkyl, cycloalkyl and aryl, wherein haloalkyl, alkyl, aralkyl, cycloalkyl, and aryl each is independently optionally substituted with one or more radicals selected from the group consisting of alkylthio, nitro and alkylsulfonyl; and

R^7 is one or more radicals selected from the group consisting of hydrido, halo, alkyl, aralkyl, alkoxy, aryloxy, heteroaryloxy, aralkyloxy, heteroaralkyloxy, haloalkyl, haloalkoxy, alkylamino, arylamino, aralkylamino, heteroarylamino, heteroarylalkylamino, nitro, amino, aminosulfonyl, alkylaminosulfonyl, arylaminosulfonyl, heteroarylaminosulfonyl, aralkylaminosulfonyl, heteroaralkylaminosulfonyl, heterocyclosulfonyl, alkylsulfonyl, optionally substituted aryl, optionally substituted heteroaryl, aralkylcarbonyl, heteroarylcarbonyl, arylcarbonyl, aminocarbonyl, and alkylcarbonyl; or wherein R^7 together with ring A forms a naphthyl radical;

or an isomer or pharmaceutically acceptable salt thereof.

The COX-2 inhibitor may also be a compound of Formula II, wherein:

Y is selected from the group consisting of oxygen and sulfur;

R^5 is selected from the group consisting of carboxyl, lower alkyl, lower aralkyl and lower alkoxycarbonyl;

R^6 is selected from the group consisting of lower haloalkyl, lower cycloalkyl and phenyl; and

R^7 is one or more radicals selected from the group of consisting of hydrido, halo, lower alkyl, lower alkoxy, lower haloalkyl, lower haloalkoxy, lower alkylamino, nitro, amino, aminosulfonyl, lower alkylaminosulfonyl, 5-membered heteroarylalkylaminosulfonyl, 6-membered heteroarylalkylaminosulfonyl, lower aralkylaminosulfonyl, 5-membered nitrogen-containing heterocyclosulfonyl, 6-membered-nitrogen containing heterocyclosulfonyl, lower alkylsulfonyl, optionally substituted phenyl, lower aralkylcarbonyl, and lower alkylcarbonyl; or

wherein R^7 together with ring A forms a naphthyl radical;

or an isomer or pharmaceutically acceptable salt thereof.

The COX-2 inhibitor may also be a compound of Formula II, wherein:

R^5 is carboxyl;

R^6 is lower haloalkyl; and

R^7 is one or more radicals selected from the group consisting of hydrido, halo, lower alkyl, lower haloalkyl, lower haloalkoxy, lower alkylamino, amino, aminosulfonyl, lower alkylaminosulfonyl, 5-membered heteroarylalkylaminosulfonyl, 6-membered heteroarylalkylaminosulfonyl, lower aralkylaminosulfonyl, lower alkylsulfonyl, 6-membered nitrogen-containing heterocyclosulfonyl, optionally substituted phenyl, lower aralkylcarbonyl, and lower alkylcarbonyl; or wherein R^7 together with ring A forms a naphthyl radical;

or an isomer or pharmaceutically acceptable salt thereof.

The COX-2 inhibitor may also be a compound of Formula II, wherein:

R^6 is selected from the group consisting of fluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, difluoroethyl, difluoropropyl, dichloroethyl, dichloropropyl, difluoromethyl, and trifluoromethyl; and

R^7 is one or more radicals selected from the group consisting of hydrido, chloro, fluoro, bromo, iodo, methyl, ethyl, isopropyl, *tert*-butyl, butyl, isobutyl, pentyl, hexyl, methoxy, ethoxy, isopropyloxy, tertbutyloxy, trifluoromethyl, difluoromethyl, trifluoromethoxy, amino, N,N-dimethylamino, N,N-diethylamino, N-phenylmethylaminosulfonyl, N-phenylethylaminosulfonyl, N-(2-furylmethyl)aminosulfonyl, nitro, N,N-dimethylaminosulfonyl, aminosulfonyl, N-methylaminosulfonyl, N-ethylsulfonyl, 2,2-dimethylethylaminosulfonyl, N,N-dimethylaminosulfonyl, N-(2-methylpropyl)aminosulfonyl, N-morpholinosulfonyl, methylsulfonyl, benzylcarbonyl, 2,2-dimethylpropylcarbonyl, phenylacetyl and phenyl; or wherein R^2 together with ring A forms a naphthyl radical;

or an isomer or pharmaceutically acceptable salt thereof.

The COX-2 inhibitor may also be a compound of Formula II, wherein:

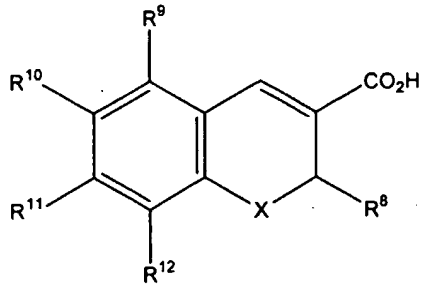
R^6 is selected from the group consisting trifluoromethyl and pentafluoroethyl;

and

R^7 is one or more radicals selected from the group consisting of hydrido, chloro, fluoro, bromo, iodo, methyl, ethyl, isopropyl, *tert*-butyl, methoxy, trifluoromethyl, trifluoromethoxy, N-phenylmethylaminosulfonyl, N-phenylethylaminosulfonyl, N-(2-furylmethyl)aminosulfonyl, N,N-dimethylaminosulfonyl, N-methylaminosulfonyl, N-(2,2-dimethylethyl)aminosulfonyl, dimethylaminosulfonyl, 2-methylpropylaminosulfonyl, N-morpholinosulfonyl, methylsulfonyl, benzylcarbonyl, and phenyl; or wherein R^7 together with ring A forms a naphthyl radical;

or an isomer or prodrug thereof.

The COX-2 inhibitor of the present invention can also be a compound having the structure of Formula III:



III

wherein:

X is selected from the group consisting of O and S;

R^8 is lower haloalkyl;

R^9 is selected from the group consisting of hydrido, and halo;

R^{10} is selected from the group consisting of hydrido, halo, lower alkyl, lower haloalkoxy, lower alkoxy, lower aralkylcarbonyl, lower dialkylaminosulfonyl, lower alkylaminosulfonyl, lower aralkylaminosulfonyl, lower heteroaralkylaminosulfonyl, 5-membered nitrogen-containing heterocyclosulfonyl, and 6- membered nitrogen-

containing heterocyclosulfonyl;

R^{11} is selected from the group consisting of hydrido, lower alkyl, halo, lower alkoxy, and aryl; and

R^{12} is selected from the group consisting of the group consisting of hydrido, halo, lower alkyl, lower alkoxy, and aryl;

or an isomer or prodrug thereof.

The COX-2 inhibitor can also be a compound of having the structure of Formula III, wherein

R^{8} is selected from the group consisting of trifluoromethyl and pentafluoroethyl;

R^{9} is selected from the group consisting of hydrido, chloro, and fluoro;

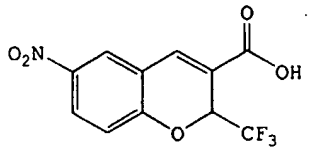
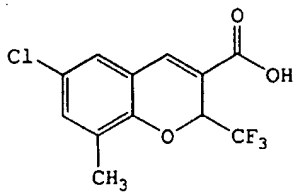
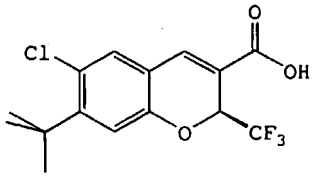
R^{10} is selected from the group consisting of hydrido, chloro, bromo, fluoro, iodo, methyl, tert-butyl, trifluoromethoxy, methoxy, benzylcarbonyl, dimethylaminosulfonyl, isopropylaminosulfonyl, methylaminosulfonyl, benzylaminosulfonyl, phenylethylaminosulfonyl, methylpropylaminosulfonyl, methylsulfonyl, and morpholinosulfonyl;

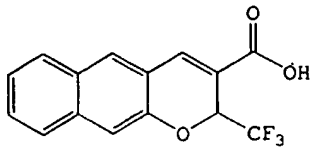
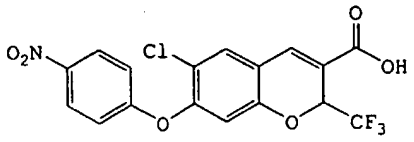
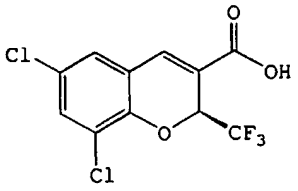
R^{11} is selected from the group consisting of hydrido, methyl, ethyl, isopropyl, tert-butyl, chloro, methoxy, diethylamino, and phenyl; and

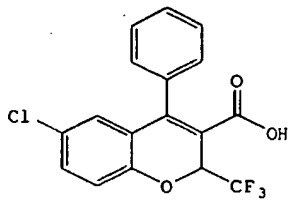
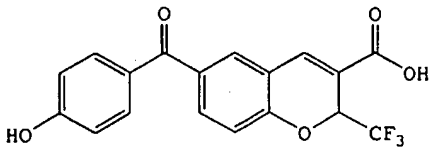
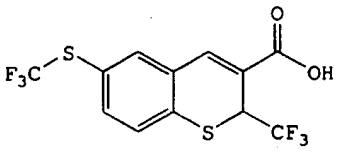
R^{12} is selected from the group consisting of hydrido, chloro, bromo, fluoro, methyl, ethyl, tert-butyl, methoxy, and phenyl;

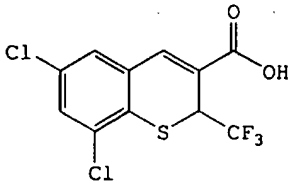
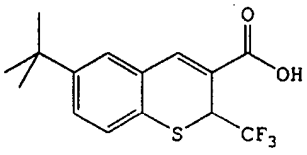
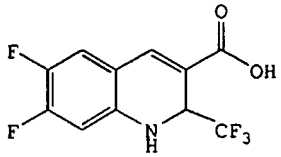
or an isomer or prodrug thereof.

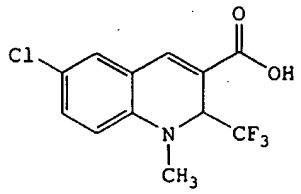
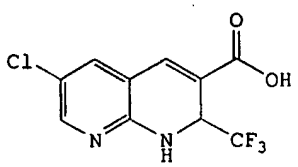
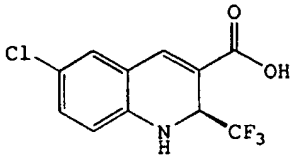
Table 1. Examples of Chromene COX-2 Inhibitors as Embodiments

Compound Number	Structural Formula
B-3	 6-Nitro-2-trifluoromethyl-2H-1 -benzopyran-3-carboxylic acid
B-4	 6-Chloro-8-methyl-2-trifluoromethyl -2H-1-benzopyran-3-carboxylic acid
B-5	 ((S)-6-Chloro-7-(1,1-dimethylethyl)-2-(trifluo romethyl-2H-1-benzopyran-3-carboxylic acid

Compound Number	Structural Formula
B-6	 2-Trifluoromethyl-2H-naphtho[2,3-b] pyran-3-carboxylic acid
B-7	 6-Chloro-7-(4-nitrophenoxy)-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid
B-8	 ((S)-6,8-Dichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid

Compound Number	Structural Formula
B-9	 6-Chloro-2-(trifluoromethyl)-4-phenyl-2H-1-benzopyran-3-carboxylic acid
B-10	 6-(4-Hydroxybenzoyl)-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid
B-11	 2-(Trifluoromethyl)-6-[(trifluoromethyl)thio]-2H-1-benzothiopyran-3-carboxylic acid

Compound Number	Structural Formula
B-12	 6,8-Dichloro-2-trifluoromethyl-2H-1-benzothiopyran-3-carboxylic acid
B-13	 6-(1,1-Dimethylethyl)-2-(trifluoromethyl)-2H-1-benzothiopyran-3-carboxylic acid
B-14	 6,7-Difluoro-1,2-dihydro-2-(trifluoro methyl)-3-quinolinecarboxylic acid

Compound Number	Structural Formula
B-15	 6-Chloro-1,2-dihydro-1-methyl-2-(trifluoro methyl)-3-quinolinecarboxylic acid
B-16	 6-Chloro-2-(trifluoromethyl)-1,2-dihydro [1,8]naphthyridine-3-carboxylic acid
B-17	 ((S)-6-Chloro-1,2-dihydro-2-(trifluoro methyl)-3-quinolinecarboxylic acid

Specific compounds that are useful for the COX-2 inhibitor include:

a1) 8-acetyl-3-(4-fluorophenyl)-2-(4-methylsulfonyl)phenyl-imidazo(1,2-a)pyridine;

a2) 5,5-dimethyl-4-(4-methylsulfonyl)phenyl-3-phenyl-2-(5H)-furanone;

a3) 5-(4-fluorophenyl)-1-[4-(methylsulfonyl)phenyl]-3-(trifluoromethyl)pyrazole;

a4) 4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-1-phenyl-3-(trifluoromethyl)pyrazole;

a5) 4-(5-(4-chlorophenyl)-3-(4-methoxyphenyl)-1H-pyrazol-1-yl)benzenesulfonamide;

a6) 4-(3,5-bis(4-methylphenyl)-1H-pyrazol-1-yl)benzenesulfonamide;

a7) 4-(5-(4-chlorophenyl)-3-phenyl-1H-pyrazol-1-yl)benzenesulfonamide;

a8) 4-(3,5-bis(4-methoxyphenyl)-1H-pyrazol-1-yl)benzenesulfonamide;

a9) 4-(5-(4-chlorophenyl)-3-(4-methylphenyl)-1H-pyrazol-1-yl)benzenesulfonamide;

a10) 4-(5-(4-chlorophenyl)-3-(4-nitrophenyl)-1H-pyrazol-1-yl)benzenesulfonamide;

b1) 4-(5-(4-chlorophenyl)-3-(5-chloro-2-thienyl)-1H-pyrazol-1-yl)benzenesulfonamide;

b2) 4-(4-chloro-3,5-diphenyl-1H-pyrazol-1-yl)benzenesulfonamide

b3) 4-[5-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

b4) 4-[5-phenyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

b5) 4-[5-(4-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

b6) 4-[5-(4-methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

b7) 4-[5-(4-chlorophenyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

b8) 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

b9) 4-[4-chloro-5-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

b10) 4-[3-(difluoromethyl)-5-(4-methylphenyl)-1H-pyrazol-1-yl]benzenesulfonamide;

c1) 4-[3-(difluoromethyl)-5-phenyl-1H-pyrazol-1-yl]benzenesulfonamide;

c2) 4-[3-(difluoromethyl)-5-(4-methoxyphenyl)-1H-pyrazol-1-

yl]benzenesulfonamide;

c3) 4-[3-cyano-5-(4-fluorophenyl)-1H-pyrazol-1-yl]benzenesulfonamide;

c4) 4-[3-(difluoromethyl)-5-(3-fluoro-4-methoxyphenyl)-1H-pyrazol-1-yl]benzenesulfonamide;

c5) 4-[5-(3-fluoro-4-methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

c6) 4-[4-chloro-5-phenyl-1H-pyrazol-1-yl]benzenesulfonamide;

c7) 4-[5-(4-chlorophenyl)-3-(hydroxymethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

c8) 4-[5-(4-(N,N-dimethylamino)phenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

c9) 5-(4-fluorophenyl)-6-[4-(methylsulfonyl)phenyl]spiro[2.4]hept-5-ene;

c10) 4-[6-(4-fluorophenyl)spiro[2.4]hept-5-en-5-yl]benzenesulfonamide;

d1) 6-(4-fluorophenyl)-7-[4-(methylsulfonyl)phenyl]spiro[3.4]oct-6-ene;

d2) 5-(3-chloro-4-methoxyphenyl)-6-[4-(methylsulfonyl)phenyl]spiro[2.4]hept-5-ene;

d3) 4-[6-(3-chloro-4-methoxyphenyl)spiro[2.4]hept-5-en-5-yl]benzenesulfonamide;

d4) 5-(3,5-dichloro-4-methoxyphenyl)-6-[4-(methylsulfonyl)phenyl]spiro[2.4]hept-5-ene;

d5) 5-(3-chloro-4-fluorophenyl)-6-[4-(methylsulfonyl)phenyl]spiro[2.4]hept-5-ene;

d6) 4-[6-(3,4-dichlorophenyl)spiro[2.4]hept-5-en-5-yl]benzenesulfonamide;

d7) 2-(3-chloro-4-fluorophenyl)-4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)thiazole;

d8) 2-(2-chlorophenyl)-4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)thiazole;

d9) 5-(4-fluorophenyl)-4-(4-methylsulfonylphenyl)-2-methylthiazole;

d10) 4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-2-trifluoromethylthiazole;

e1) 4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-2-(2-thienyl)thiazole;

e2) 4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-2-benzylaminothiazole;

e3) 4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-2-(1-propylamino)thiazole;

e4) 2-[(3,5-dichlorophenoxy)methyl)-4-(4-fluorophenyl)-5-[4-

(methylsulfonyl)phenyl]thiazole;

e5) 5-(4-fluorophenyl)-4-(4-methylsulfonylphenyl)-2-trifluoromethylthiazole;

e6) 1-methylsulfonyl-4-[1,1-dimethyl-4-(4-fluorophenyl)cyclopenta-2,4-dien-3-yl]benzene;

e7) 4-[4-(4-fluorophenyl)-1,1-dimethylcyclopenta-2,4-dien-3-yl]benzenesulfonamide;

e8) 5-(4-fluorophenyl)-6-[4-(methylsulfonyl)phenyl]spiro[2.4]hepta-4,6-diene;

e9) 4-[6-(4-fluorophenyl)spiro[2.4]hepta-4,6-dien-5-yl]benzenesulfonamide;

e10) 6-(4-fluorophenyl)-2-methoxy-5-[4-(methylsulfonyl)phenyl]-pyridine-3-carbonitrile;

f1) 2-bromo-6-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-pyridine-3-carbonitrile;

f2) 6-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-2-phenyl-pyridine-3-carbonitrile;

f3) 4-[2-(4-methylpyridin-2-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;

f4) 4-[2-(5-methylpyridin-3-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;

f5) 4-[2-(2-methylpyridin-3-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;

f6) 3-[1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazol-2-yl]pyridine;

f7) 2-[1-[4-(methylsulfonyl)phenyl-4-(trifluoromethyl)-1H-imidazol-2-yl]pyridine;

f8) 2-methyl-4-[1-[4-(methylsulfonyl)phenyl-4-(trifluoromethyl)-1H-imidazol-2-yl]pyridine;

f9) 2-methyl-6-[1-[4-(methylsulfonyl)phenyl-4-(trifluoromethyl)-1H-imidazol-2-yl]pyridine;

f10) 4-[2-(6-methylpyridin-3-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;

g1) 2-(3,4-difluorophenyl)-1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazole;

g2) 4-[2-(4-methylphenyl)-4-(trifluoromethyl)-1H-imidazol-1-

yl]benzenesulfonamide;

g3) 2-(4-chlorophenyl)-1-[4-(methylsulfonyl)phenyl]-4-methyl-1H-imidazole;

g4) 2-(4-chlorophenyl)-1-[4-(methylsulfonyl)phenyl]-4-phenyl-1H-imidazole;

g5) 2-(4-chlorophenyl)-4-(4-fluorophenyl)-1-[4-(methylsulfonyl)phenyl]-1H-imidazole;

g6) 2-(3-fluoro-4-methoxyphenyl)-1-[4-(methylsulfonyl)phenyl-4-(trifluoromethyl)-1H-imidazole;

g7) 1-[4-(methylsulfonyl)phenyl]-2-phenyl-4-trifluoromethyl-1H-imidazole;

g8) 2-(4-methylphenyl)-1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazole;

g9) 4-[2-(3-chloro-4-methylphenyl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;

g10) 2-(3-fluoro-5-methylphenyl)-1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazole;

h1) 4-[2-(3-fluoro-5-methylphenyl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;

h2) 2-(3-methylphenyl)-1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazole;

h3) 4-[2-(3-methylphenyl)-4-trifluoromethyl-1H-imidazol-1-yl]benzenesulfonamide;

h4) 1-[4-(methylsulfonyl)phenyl]-2-(3-chlorophenyl)-4-trifluoromethyl-1H-imidazole;

h5) 4-[2-(3-chlorophenyl)-4-trifluoromethyl-1H-imidazol-1-yl]benzenesulfonamide;

h6) 4-[2-phenyl-4-trifluoromethyl-1H-imidazol-1-yl]benzenesulfonamide;

h7) 4-[2-(4-methoxy-3-chlorophenyl)-4-trifluoromethyl-1H-imidazol-1-yl]benzenesulfonamide;

h8) 1-allyl-4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-5-(trifluoromethyl)-1H-pyrazole;

h10) 4-[1-ethyl-4-(4-fluorophenyl)-5-(trifluoromethyl)-1H-pyrazol-3-yl]benzenesulfonamide;

i1) N-phenyl-[4-(4-luorophenyl)-3-[4-(methylsulfonyl)phenyl]-5-(trifluoromethyl)-1H-pyrazol-1-yl]acetamide;

i2) ethyl [4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-5-(trifluoromethyl)-1H-

pyrazol-1-yl]acetate;

i3) 4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-1-(2-phenylethyl)-1H-pyrazole;

i4) 4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-1-(2-phenylethyl)-5-(trifluoromethyl)pyrazole;

i5) 1-ethyl-4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-5-(trifluoromethyl)-1H-pyrazole;

i6) 5-(4-fluorophenyl)-4-(4-methylsulfonylphenyl)-2-trifluoromethyl-1H-imidazole;

i7) 4-[4-(methylsulfonyl)phenyl]-5-(2-thiophenyl)-2-(trifluoromethyl)-1H-imidazole;

i8) 5-(4-fluorophenyl)-2-methoxy-4-[4-(methylsulfonyl)phenyl]-6-(trifluoromethyl)pyridine;

i9) 2-ethoxy-5-(4-fluorophenyl)-4-[4-(methylsulfonyl)phenyl]-6-(trifluoromethyl)pyridine;

i10) 5-(4-fluorophenyl)-4-[4-(methylsulfonyl)phenyl]-2-(2-propynyloxy)-6-(trifluoromethyl)pyridine;

j1) 2-bromo-5-(4-fluorophenyl)-4-[4-(methylsulfonyl)phenyl]-6-(trifluoromethyl)pyridine;

j2) 4-[2-(3-chloro-4-methoxyphenyl)-4,5-difluorophenyl]benzenesulfonamide;

j3) 1-(4-fluorophenyl)-2-[4-(methylsulfonyl)phenyl]benzene;

j4) 5-difluoromethyl-4-(4-methylsulfonylphenyl)-3-phenylisoxazole;

j5) 4-[3-ethyl-5-phenylisoxazol-4-yl]benzenesulfonamide;

j6) 4-[5-difluoromethyl-3-phenylisoxazol-4-yl]benzenesulfonamide;

j7) 4-[5-hydroxymethyl-3-phenylisoxazol-4-yl]benzenesulfonamide;

j8) 4-[5-methyl-3-phenyl-isoxazol-4-yl]benzenesulfonamide;

j9) 1-[2-(4-fluorophenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;

j10) 1-[2-(4-fluoro-2-methylphenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;

k1) 1-[2-(4-chlorophenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;

k2) 1-[2-(2,4-dichlorophenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;

k3) 1-[2-(4-trifluoromethylphenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;

k4) 1-[2-(4-methylthiophenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;

k5) 1-[2-(4-fluorophenyl)-4,4-dimethylcyclopenten-1-yl]-4-(methylsulfonyl)benzene;

k6) 4-[2-(4-fluorophenyl)-4,4-dimethylcyclopenten-1-yl]benzenesulfonamide;

k7) 1-[2-(4-chlorophenyl)-4,4-dimethylcyclopenten-1-yl]-4-(methylsulfonyl)benzene;

k8) 4-[2-(4-chlorophenyl)-4,4-dimethylcyclopenten-1-yl]benzenesulfonamide;

k9) 4-[2-(4-fluorophenyl)cyclopenten-1-yl]benzenesulfonamide;

k10) 4-[2-(4-chlorophenyl)cyclopenten-1-yl]benzenesulfonamide;

l1) 1-[2-(4-methoxyphenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;

l2) 1-[2-(2,3-difluorophenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;

l3) 4-[2-(3-fluoro-4-methoxyphenyl)cyclopenten-1-yl]benzenesulfonamide;

l4) 1-[2-(3-chloro-4-methoxyphenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;

l5) 4-[2-(3-chloro-4-fluorophenyl)cyclopenten-1-yl]benzenesulfonamide;

l6) 4-[2-(2-methylpyridin-5-yl)cyclopenten-1-yl]benzenesulfonamide;

l7) ethyl 2-[4-(4-fluorophenyl)-5-[4-(methylsulfonyl) phenyl]oxazol-2-yl]-2-benzyl-acetate;

l8) 2-[4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]oxazol-2-yl]acetic acid;

l9) 2-(*tert*-butyl)-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]oxazole;

l10) 4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-2-phenyloxazole;

m1) 4-(4-fluorophenyl)-2-methyl-5-[4-(methylsulfonyl)phenyl]oxazole; and

m2) 4-[5-(3-fluoro-4-methoxyphenyl)-2-trifluoromethyl-4-oxazolyl]benzenesulfonamide.

m3) 6-chloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

m4) 6-chloro-7-methyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

m5) 8-(1-methylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

m6) 6-chloro-7-(1,1-dimethylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

m7) 6-chloro-8-(1-methylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

m8) 2-trifluoromethyl-3H-naphthopyran-3-carboxylic acid ;

m9) 7-(1,1-dimethylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

m10) 6-bromo-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

n1) 8-chloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

n2) 6-trifluoromethoxy-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

n3) 5,7-dichloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

n4) 8-phenyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

n5) 7,8-dimethyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

n6) 6,8-bis(dimethylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

n7) 7-(1-methylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

n8) 7-phenyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

n9) 6-chloro-7-ethyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

n10) 6-chloro-8-ethyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

o1) 6-chloro-7-phenyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

o2) 6,7-dichloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

o3) 6,8-dichloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

o4) 2-trifluoromethyl-3H-naptho[2,1-b]pyran-3-carboxylic acid;

o5) 6-chloro-8-methyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

o6) 8-chloro-6-methyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

o7) 8-chloro-6-methoxy-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

o8) 6-bromo-8-chloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

o9) 8-bromo-6-fluoro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

o10) 8-bromo-6-methyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

p1) 8-bromo-5-fluoro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

p2) 6-chloro-8-fluoro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

p3) 6-bromo-8-methoxy-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

p4) 6-[[(phenylmethyl)amino]sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

p5) 6-[(dimethylamino)sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

p6) 6-[(methylamino)sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

p7) 6-[(4-morpholino)sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

p8) 6-[(1,1-dimethylethyl)aminosulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

p9) 6-[(2-methylpropyl)aminosulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

p10) 6-methylsulfonyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

q1) 8-chloro-6-[[(phenylmethyl)amino]sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

q2) 6-phenylacetyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

q3) 6,8-dibromo-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

q4) 8-chloro-5,6-dimethyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

q5) 6,8-dichloro-(*S*)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

q6) 6-benzylsulfonyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

q7) 6-[[N-(2-furylmethyl)amino]sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

q8) 6-[[N-(2-phenylethyl)amino]sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

q9) 6-iodo-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

q10) 7-(1,1-dimethylethyl)-2-pentafluoroethyl-2H-1-benzopyran-3-carboxylic acid;

r1) 5,5-dimethyl-3-(3-fluorophenyl)-4-(4-methyl-sulphonyl-2(5H)-fluranone;

r2) 6-chloro-2-trifluoromethyl-2H-1-benzothiopyran-3-carboxylic acid;

r3) 4-[5-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

r4) 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

r5) 4-[5-(3-fluoro-4-methoxyphenyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

r6) 3-[1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazol-2-yl]pyridine;

r7) 2-methyl-5-[1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazol-2-yl]pyridine;

r8) 4-[2-(5-methylpyridin-3-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;

r9) 4-[5-methyl-3-phenylisoxazol-4-yl]benzenesulfonamide;

r10) 4-[5-hydroxymethyl-3-phenylisoxazol-4-yl]benzenesulfonamide;

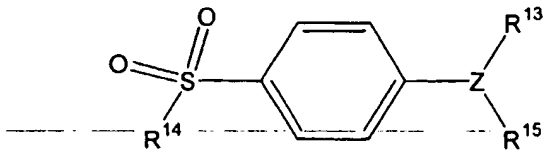
s1) [2-trifluoromethyl-5-(3,4-difluorophenyl)-4-oxazolyl]benzenesulfonamide;

s2) 4-[2-methyl-4-phenyl-5-oxazolyl]benzenesulfonamide; or

s3) 4-[5-(3-fluoro-4-methoxyphenyl-2-trifluoromethyl)-4-oxazolyl]benzenesulfonamide;

or a pharmaceutically acceptable salt or prodrug thereof.

In a further preferred embodiment of the invention the cyclooxygenase inhibitor can be selected from the class of tricyclic COX-2 inhibitors represented by the general structure of Formula IV:



IV

wherein:

Z is selected from the group consisting of partially unsaturated or unsaturated heterocyclyl and partially unsaturated or unsaturated carbocyclic rings;

R^{13} is selected from the group consisting of heterocyclyl, cycloalkyl, cycloalkenyl and aryl, wherein R^{13} is optionally substituted at a substitutable position

with one or more radicals selected from alkyl, haloalkyl, cyano, carboxyl, alkoxycarbonyl, hydroxyl, hydroxyalkyl, haloalkoxy, amino, alkylamino, arylamino, nitro, alkoxyalkyl, alkylsulfinyl, halo, alkoxy and alkylthio;

R^{14} is selected from the group consisting of methyl or amino; and

R^{15} is selected from the group consisting of a radical selected from H, halo, alkyl, alkenyl, alkynyl, oxo, cyano, carboxyl, cyanoalkyl, heterocyclyloxy, alkyloxy, alkylthio, alkylcarbonyl, cycloalkyl, aryl, haloalkyl, heterocyclyl, cycloalkenyl, aralkyl, heterocyclylalkyl, acyl, alkylthioalkyl, hydroxyalkyl, alkoxycarbonyl, arylcarbonyl, aralkylcarbonyl, aralkenyl, alkoxyalkyl, arylthioalkyl, aryloxyalkyl, aralkylthioalkyl, aralkoxyalkyl, alkoxyaralkoxyalkyl, alkoxycarbonylalkyl, aminocarbonyl, aminocarbonylalkyl, alkylaminocarbonyl, N- arylaminocarbonyl, N-alkyl-N-arylaminocarbonyl, alkylaminocarbonylalkyl, carboxyalkyl, alkylamino, N-arylamino, N-aralkylamino, N-alkyl-N-aralkylamino, N-alkyl-N-arylamino, aminoalkyl, alkylaminoalkyl, N-arylaminoalkyl, N-aralkylaminoalkyl, N-alkyl-N-aralkylaminoalkyl, N-alkyl-N-arylaminoalkyl, aryloxy, aralkoxy, arylthio, aralkylthio, alkylsulfinyl, alkylsulfonyl, aminosulfonyl, alkylaminosulfonyl, N-arylaminosulfonyl, arylsulfonyl, N-alkyl-N-arylaminosulfonyl;

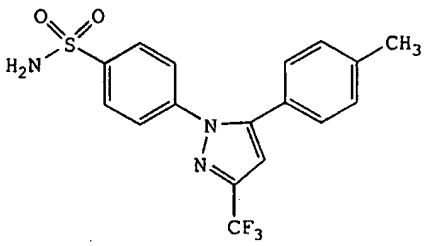
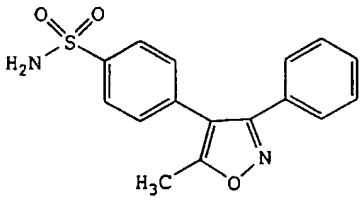
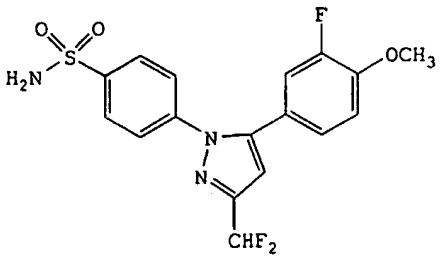
or a prodrug thereof.

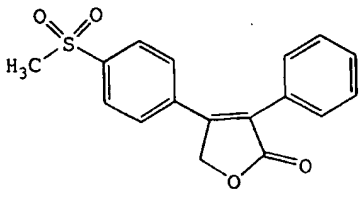
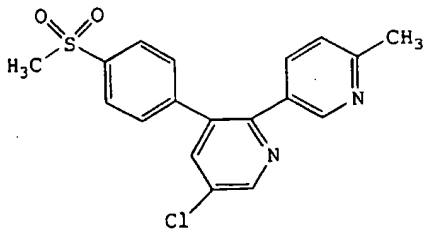
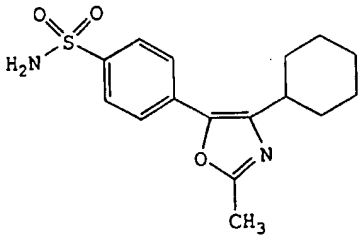
In a preferred embodiment of the invention the COX-2 inhibitor represented by the above Formula IV is selected from the group of compounds, illustrated in Table 2, which includes celecoxib (B-18), valdecoxib (B-19), deracoxib (B-20), rofecoxib (B-21), etoricoxib (MK-663; B-22), JTE-522 (B-23), or a prodrug thereof.

Additional information about selected examples of the COX-2 inhibitors discussed above can be found as follows: celecoxib (CAS RN 169590-42-5, C-2779, SC-58653, and in U.S. Patent No. 5,466,823); deracoxib (CAS RN 169590-41-4); rofecoxib (CAS RN 162011-90-7); compound B-24 (U.S. Patent No. 5,840,924); compound B-26

(WO 00/25779); and etoricoxib (CAS RN 202409-33-4, MK-663, SC-86218, and in WO 98/03484).

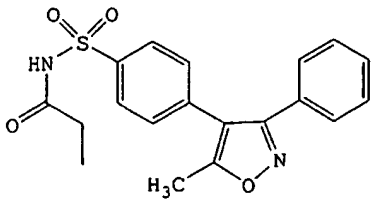
Table 2. Examples of Tricyclic COX-2 Inhibitors as Embodiments

Compound Number	Structural Formula
B-18	
B-19	
B-20	

Compound Number	Structural Formula
B-21	
B-22	
B-23	

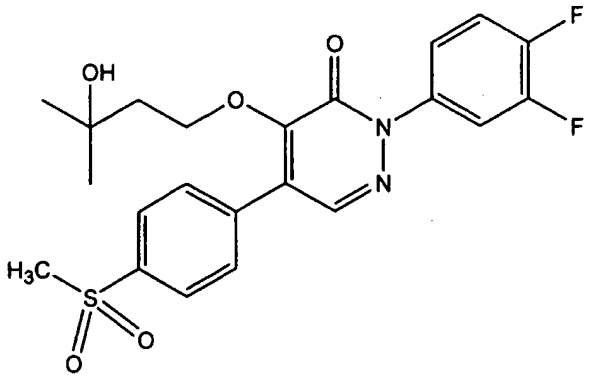
In a more preferred embodiment of the invention, the COX-2 inhibitor is selected from the group consisting of celecoxib, rofecoxib and etoricoxib. In a preferred embodiment of the invention, parecoxib (U.S. Patent No. 5,932,598), having the structure shown in B-24, which is a therapeutically effective prodrug of the tricyclic

COX-2 inhibitor valdecoxib, B-19, (U.S. Patent No. 5,633,272), may be advantageously employed as a source of a cyclooxygenase inhibitor. A preferred form of parecoxib is sodium parecoxib.



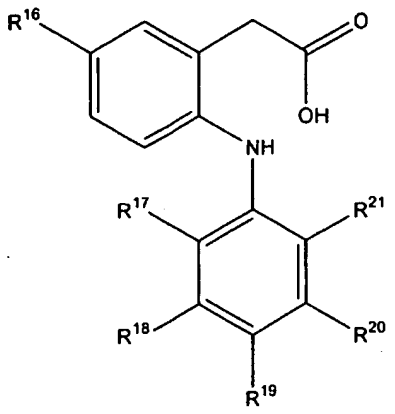
B-24

In another preferred embodiment of the invention, the compound ABT-963 having the formula B-25 that has been previously described in International Publication number WO 00/24719, is another tricyclic COX-2 inhibitor which may be advantageously employed.



B-25

In a further preferred embodiment of the invention the cyclooxygenase inhibitor can be selected from the class of phenylacetic acid derivative COX-2 inhibitors represented by the general structure of Formula V:



V

wherein R^{16} is methyl or ethyl;

R^{17} is chloro or fluoro;

R^{18} is hydrogen or fluoro;

R^{19} is hydrogen, fluoro, chloro, methyl, ethyl, methoxy, ethoxy or hydroxy;

R^{20} is hydrogen or fluoro; and

R^{21} is chloro, fluoro, trifluoromethyl or methyl,

provided that R^{17}, R^{18}, R^{19} and R^{20} are not all fluoro when R^{16} is ethyl and R^{19} is H.

A particularly preferred phenylacetic acid derivative COX-2 inhibitor that is described in WO 99/11605 is a compound that has the designation of COX189 (CAS RN 346670-74-4), and that has the structure shown in Formula V,

wherein R^{16} is ethyl;

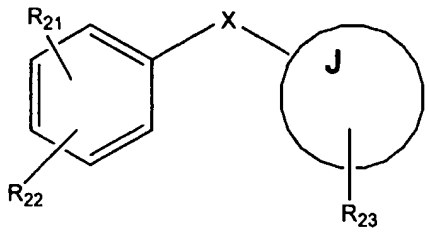
R^{17} and R^{19} are chloro;

R^{18} and R^{20} are hydrogen; and

R^{21} is methyl.

Compounds that have a structure similar to that shown in Formula V, which can serve as the COX-2 inhibitor of the present invention, are described in U.S. Patent Nos. 6,310,099 and 6,291,523.

Other preferred COX-2 inhibitors that can be used in the present invention have the general structure shown in formula VI, where the J group is a carbocycle or a heterocycle. Particularly preferred embodiments have the structure:



VI

where:

X is O; J is 1-phenyl; R_{21} is 2-$NHSO_2CH_3$; R_{22} is 4-NO_2; and there is no R_{23} group, (nimesulide); and

X is O; J is 1-oxo-inden-5-yl; R_{21} is 2-F; R_{22} is 4-F; and R_{23} is 6-$NHSO_2CH_3$, (flosulide); and

X is O; J is cyclohexyl; R_{21} is 2-$NHSO_2CH_3$; R_{22} is 5-NO_2; and there is no R_{23} group, (NS-398); and

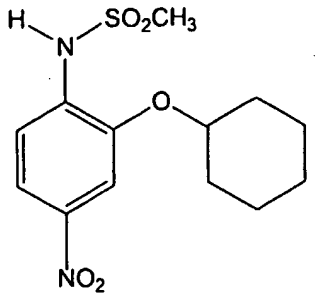
X is S; J is 1-oxo-inden-5-yl; R_{21} is 2-F; R_{22} is 4-F; and R_{23} is 6-$N^-SO_2CH_3 \cdot Na^+$, (L-745337); and

X is S; J is thiophen-2-yl; R_{21} is 4-F; there is no R_{22} group; and R_{23} is 5-$NHSO_2CH_3$, (RWJ-63556); and

X is O; J is 2-oxo-5(R)-methyl-5-(2,2,2-trifluoroethyl)furan-(5H)-3-yl; R_{21} is 3-F; R_{22} is 4-F; and R_{23} is 4-(p-SO_2CH_3)C_6H_4, (L-784512).

Further information on the applications of N-(2-cyclohexyloxynitrophenyl)methane sulfonamide (NS-398, CAS RN 123653-11-2), having a structure as shown in formula B-26, have been described by, for example, Yoshimi, N. *et al.*, in *Japanese J.*

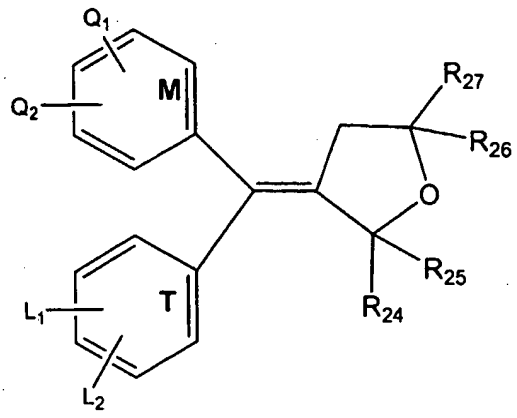
*Cancer Res., 90(4):*406 - 412 (1999); Falgueyret, J.-P. *et al.,* in *Science Spectra,* available at: http://www.gbhap.com/Science_Spectra/20-1-article.htm (06/06/2001); and Iwata, K. *et al.,* in *Jpn. J. Pharmacol., 75(2):*191 - 194 (1997).



B-26

An evaluation of the antiinflammatory activity of the COX-2 inhibitor, RWJ 63556, in a canine model of inflammation, was described by Kirchner *et al.,* in *J Pharmacol Exp Ther 282*, 1094-1101 (1997).

Other materials that can serve as he COX-2 inhibitor of the present invention include diarylmethylidenefuran derivatives that are described in U.S. Patent No. 6,180,651. Such diarylmethylidenefuran derivatives have the general formula shown below in formula **VII**:



VII

wherein:

the rings T and M independently are:

a phenyl radical,

a naphtyl radical,

a radical derived from a heterocycle comprising 5 to 6 members and possessing from 1 to 4 heteroatoms, or

a radical derived from a saturated hydrocarbon ring having from 3 to 7 carbon atoms;

at least one of the substituents Q_1, Q_2, L_1 or L_2 is:

an --$S(O)_n$ --R group, in which n is an integer equal to 0, 1 or 2 and R is

a lower alkyl radical having 1 to 6 carbon atoms, or

a lower haloalkyl radical having 1 to 6 carbon atoms, or

an -SO_2NH_2 group;

and is located in the para position,

the others independently being:

a hydrogen atom,

a halogen atom,

a lower alkyl radical having 1 to 6 carbon atoms,

a trifluoromethyl radical, or

a lower O-alkyl radical having 1 to 6 carbon atoms, or

Q_1 and Q_2 or L_1 and L_2 are a methylenedioxy group; and

R_{24}, R_{25}, R_{26} and R_{27} independently are:

a hydrogen atom,

a halogen atom,

a lower alkyl radical having 1 to 6 carbon atoms,

a lower haloalkyl radical having 1 to 6 carbon atoms, or

an aromatic radical selected from the group consisting of phenyl, naphthyl, thienyl, furyl and pyridyl; or,

R_{24}, R_{25} or R_{26}, R_{27} are an oxygen atom, or

R_{24}, R_{25} or R_{26}, R_{27}, together with the carbon atom to which they are attached, form a saturated hydrocarbon ring having from 3 to 7 carbon atoms;

or an isomer or prodrug thereof.

Particular materials that are included in this family of compounds, and which can serve as the COX-2 inhibitor in the present invention, include N-(2-cyclohexyloxynitrophenyl)methane sulfonamide, and (E)-4-[(4-methylphenyl)(tetrahydro-2-oxo-3-furanylidene) methyl]benzenesulfonamide.

COX-2 inhibitors that are useful in the present invention include darbufelone (Pfizer), CS-502 (Sankyo), LAS 34475 (Almirall Profesfarma), LAS 34555 (Almirall Profesfarma), S-33516 (Servier, see *Current Drugs Headline News*, at http://www.current-drugs.com/NEWS/Inflam1.htm, 10/04/2001), , BMS-347070 (Bristol Myers Squibb, described in U.S. Patent No. 6,180,651), MK-966 (Merck), L-783003 (Merck), T-614 (Toyama), D-1367 (Chiroscience), L-748731 (Merck), CT3 (Atlantic Pharmaceutical), CGP-28238 (Novartis), BF-389 (Biofor/Scherer), GR-253035 (Glaxo Wellcome), 6-dioxo-9H-purin-8-yl-cinnamic acid (Glaxo Wellcome), and S-2474 (Shionogi).

COX-2 inhibitors that are useful in the invention can include the compounds that are described in U.S. Patent Nos. 6,310,079; 6,306,890 and 6,303,628 (bicycliccarbonyl indoles); U.S. Patent No. 6,300,363 (indole compounds); U.S. Patent Nos. 6,297,282 and 6,004,948 (substituted derivatives of benzosulphonamides); U.S. Patent Nos. 6,239,173, 6,169,188, 6,133,292; 6,020,343; 6,071,954; 5,981,576 ((methylsulfonyl)phenyl furanones); U.S. Patent No. 6,083,969 (diarylcycloalkano and cycloalkeno pyrazoles); U.S. Patent No. 6,222,048 (diaryl-2-(5H)-furanones; U.S. Patent No. 6,077,869 (aryl phenylhydrazines); U.S. Patent Nos. 6,071,936 and 6,001,843 (substituted pyridines); U.S. Patent No. 6,307,047 (pyridazinone compounds); U.S. Patent No. 6,140,515 (3-aryl-4-aryloxyfuran-5-ones); U.S. Patent Nos. 6,204,387 and 6,127,545 (diaryl pyridines); U.S. Patent No. 6,057,319 (3,4-

diaryl-2-hydroxy-2,5-dihydrofurans; U.S. Patent No. 6,046,236 (carbocyclic sulfonamides); and U.S. Patent Nos. 6,002,014; 5,994,381; and 5,945,539 (oxazole derivatives).

Preferred COX-2 inhibitors for the use according to the present invention include celecoxib (Celebrex®), rofecoxib (Vioxx®), meloxicam, piroxicam, deracoxib, parecoxib, valdecoxib, etoricoxib, a chromene derivative, a chroman derivative, N-(2-cyclohexyloxynitrophenyl)methane sulfonamide, COX189, ABT963, JTE-522, pharmaceutically acceptable salts, prodrugs or mixtures thereof. More preferred COX-2 inhibitors are celecoxib, parecoxib, valdecoxib, etoricoxib and rofecoxib.

According to a preferred embodiment, celecoxib (Celebrex®) or a pharmaceutically acceptable salt thereof is used. The term pharmaceutically acceptable salt includes salts that can be prepared according to known methods by those skilled in the art from the corresponding compound of the present invention, e.g. conventional metallic ion salts and organic salts.

Celecoxib can be administered at a dose of 50-1600 mg per day, preferably 200 to 600 mg, most preferably 400 mg per day. The administration can be carried out once or several times a day, preferably twice. The amount of celecoxib can be adapted depending on age, body weight and/or possible other diseases of the patient. Preferably, celecoxib is used in the form of tablets (Celebrex®) for oral administration.

Without intending to establish a certain theory as explanation for the observed effect of COX-2 inhibitors, the following mechanisms of action are taken into consideration.

There is no doubt that activation of COX-2 mediates inflammatory processes and that COX-2 is expressed in brain tissue. COX-2 can be activated by cytokines like IL-2, IL-6 and IL-10, and cytokine-activated COX-2 expression mediates further inflammatory processes. It was reported that IL-2 and soluble IL-2 receptors (Licino

J, Seibyl, JP, Altemus M, Charney DS, Krystal JH: Elevated levels of Interleukin-2 in neuroleptic-free schizophrenics. Am J Psychiatry 1993; 150: 1408-1410) (McAllister CG, van Kemmen DP, Rehn TJ, Miller AL, Gurklis J, Kelley ME, Yao J, Peters JL: Increases in CSF levels of Interleukin-2 in schizophrenia: effects of recurrence of psychosis and medication status. Am J Psychiatry 1995; 152: 1291-1297), soluble IL-6 receptors as a functional part of the IL-6 system (Müller N, Dobmeier P, Empel M, Riedel M, Schwarz M, Ackenheil M: Soluble IL-6 Receptors in the serum and cerebrospinal fluid of paranoid schizophrenic patients. Eur Psychiatry 1997; 12: 294-299) and IL-10 (Van Kammen DP, McAllister-Sistilli CG, Kelley ME: Relationship between immune and behavioral measures in schizophrenia. In: G. Wieselmann (ed.) Current Update in Psychoimmunology, Springer Verlag 1997; Wien, NY, pp. 51-55) are increased in the cerebrospinal fluid of schizophrenic patients - the increase of the cytokines in the CNS may be accompanied by increased COX-2 expression. The effectiveness of COX-2 inhibitors, such as celecoxib, in the treatment of schizophrenia, might be based on the finding that celecoxib down-regulates the cytokine-induced CNS COX-2 activation.

Moreover, COX-2 inhibition seems to regulate the expression of adhesion molecules (Schwarz MJ, Ackenheil M, Riedel M, Müller N: Blood-CSF-Barrier impairment as indicator for an immune process in schizophrenia. Neurosci Letters 1998; 253: 201-203). Since adhesion molecule regulation is impaired in schizophrenia, leading to dysbalance and lack of communication between the peripheral and the CNS immune system, the effects of COX-2 inhibitors, such as celecoxib, in the treatment of schizophrenia, may also be related to the adhesion molecules ICAM-1 and VCAM-1, expecially regarding the negative symptoms (Schwarz MJ, Riedel M, Gruber R, Ackenheil M, Müller N: Levels of soluble adhesion molecules in schizophrenia: Relation to psychopathology. In: N. Müller (Hrg) Psychiatry, Psychoneuroimmunology, and Viruses. Springer Verlag Wien, 1999, NY, pp. 121-130; Müller N, Ackenheil M: Immunoglobulin and albumin contents of cerebrospinal fluid in schizophrenic patients: The relationship to negative sympomatology. Schizophrenia Res 1995; 14: 223-228).

According to a further embodiment of the present invention, a COX-2 inhibitor is used

in combination with a neuroleptic drug or an antidepressant for the manufacture of a medicament for the treatment of psychiatric disorders such as schizophrenia, delusional disorders, affective disorders, autism or tic disorders. Combinations can also include a mixture of one or more COX-2 inhibitors with one or more neuroleptic agents or antidepressants. In particular, the combination of a COX-2 inhibitor with a neuroleptic drug is useful for the treatment of schizophrenia, whereas the combination of a COX-2 inhibitor with an antidepressant is applicable for the treatment of depressive disorders.

Both classical and atypical neuroleptics can be used for the add-on use according to the invention, atypical neuroleptics being preferred.

Examples of neuroleptic drugs that are useful in the present invention include, but are not limited to: butyrophenones, such as haloperidol, pimozide, and droperidol; phenothiazines, such as chlorpromazine, thioridazine, mesoridazine, trifluoperazine, perphenazine, fluphenazine, thiflupromazine, prochlorperazine, and acetophenazine; thioxanthenes, such as thiothixene and chlorprothixene; thienobenzodiazepines; dibenzodiazepines; benzisoxazoles; dibenzothiazepines; imidazolidinones; benzisothiazolyl-piperazines; dibenzoxazepines, such as loxapine; dihydroindolones, such as molindone; aripiprazole; and derivatives thereof that have antipsychotic activity.

Examples of neuroleptic drugs that are preferred for use in the present invention are shown in Table 3.

Table 3: Neuroleptic drugs

Common Name	Trade Name	Route of Adminis-tration	Form	Dosage Range and (Median)[a]
Clozapine	CLOZARIL	oral	tablets	12.5 - 900 mg/day (300 - 900 mg/day)
Olanzapine	ZYPREXA	oral	tablets	5 - 25 mg/day

				(10 - 25 mg/day)
Ziprasidone	GEODON	oral	capsules	20 - 80 mg/twice a day (80 - 160 mg/day)
Risperidone	RISPERDAL	oral	solution tablets	2 - 16 mg/day (4 - 12 mg/day)
Quetiapine fumarate	SEROQUEL	oral	tablets	50 - 900 mg/day (300 - 900 mg/day)
Sertindole	SERLECT			(4 - 24 mg/day)
Amisulpride				
Haloperidol	HALDOL	oral	tablets	1 - 100 mg/day (1 - 15 mg/day)
Haloperidol Decanoate	HALDOL Decanoate	parenteral	injection	
Haloperidol lactate	HALDOL INTENSOL	oral	solution	
		parenteral	injection	
Chlorpromazine	THORAZINE	rectal	suppositories	30 - 800 mg/day (200 - 500 mg/day)
		oral	capsules solution tablets	
		parenteral	injection	
Fluphenazine	PROLIXIN			0.5 - 40 mg/day (1 - 5 mg/day)
Fluphenazine decanoate	PROLIXIN Decanoate	parenteral	injection	(about one-half the dosage shown for oral)
Fluphenazine enanthate	PROLIXIN	parenteral	injection	(same as above)
Fluphenazine hydrochloride	PROLIXIN	oral	elixer solution tablets	
		parenteral	injection	
Thiothixene	NAVANE	oral	capsules	6 - 60 mg/day (8 - 30 mg/day)

Thiothixene hydrochloride	NAVANE	oral	solution	
		parenteral	injection	
Trifluoperazine	STELAZINE			(2 - 40 mg/day)
Perphenazine	TRILAFON	oral	solution tablets	12 - 64 mg/day (16 - 64 mg/day)
		parenteral	injection	
Perpehazine and Amitriptyline hydrochloride	ETRAFON TRIAVIL	oral	tablets	
Thioridazine	MELLARIL	oral	suspension solution tablets	150 - 800 mg/day (100 - 300 mg/day)
Mesoridazine				(30 - 400 mg/day)
Molindone	MOBAN			50 - 225 mg/day (15 - 150 mg/day)
Molindone hydrochloride	MOBAN	oral	solution	
Loxapine	LOXITANE			20 - 250 mg/day (60 - 100 mg/day)
Loxapine hydrochloride	LOXITANE	oral	solution	
		parenteral	injection	
Loxapine succinate	LOXITANE	oral	capsules	
Pimozide				(1 - 10 mg/day)
Flupenthixol				
Promazine	SPARINE			
Triflupromazine	VESPRIN			
Chlorprothixene	TARACTAN			
Droperidol	INAPSINE			
Acetophenazine	TINDAL			
Prochlorperazine	COMPAZINE			
Methotrimeprazine	NOZINAN			
Pipotiazine	PIPOTRIL			
Ziprasidone				

Hoperidone				
Zuclopenthixol				

Examples of tradenames and suppliers of selected neuroleptic drugs are as follows: clozapine (available under the tradename CLOZARIL®, from Mylan, Zenith Goldline, UDL, Novartis); olanzapine (available under the tradename ZYPREXA®, from Lilly; ziprasidone (available under the tradename GEODON®, from Pfizer); risperidone (available under the tradename RISPERDAL®, from Janssen); quetiapine fumarate (available under the tradename SEROQUEL®, from AstraZeneca); haloperidol (available under the tradename HALDOL®, from Ortho-McNeil); chlorpromazine (available under the tradename THORAZINE®, from SmithKline Beecham); fluphenazine (available under the tradename PROLIXIN®, from Apothecon, Copley, Schering, Teva, and American Pharmaceutical Partners, Pasadena); thiothixene (available under the tradename NAVANE®, from Pfizer); trifluoperazine (10-[3-(4-methyl-1-piperazinyl) propyl]-2-(trifluoromethyl) phenothiazine dihydrochloride, available under the tradename STELAZINE®, from SmithKlein Beckman); perphenazine (available under the tradename TRILAFON®, from Schering); thioridazine (available under the tradename MELLARIL®, from Novartis, Roxane, Hi-Tech, Teva, and Alpharma); molindone (available under the tradename MOBAN®, from Endo); and loxapine (available under the tradename LOXITANE® from Watson). Furthermore, benperidol (Glianimon®), perazine (Taxilan®) or melperone (Eunerpan®) may be used.

Other preferred neuroleptic drugs include promazine (available under the tradename SPARINE®), triflurpromazine (available under the tradename VESPRIN®), chlorprothixene (available under the tradename TARACTAN®), droperidol (available under the tradename INAPSINE®), acetophenazine (available under the tradename TINDAL®), prochlorperazine (available under the tradename COMPAZINE®), methotrimeprazine (available under the tradename NOZINAN®), pipotiazine

(available under the tradename PIPOTRIL®), ziprasidone, and hoperidone.

Preferred neuroleptic drugs include risperidone and aripiprazole (from Bristol Myers Squibb Company, see e.g. Stahl SM; Dopamine-system stabilizers, aripiprazole and the next generation of antipsychotics, part I, "goldilocks"-actions at dopamine receptors; J. Clin. Psychiatry 2001, 62, 11:841-842).

The most preferred neuroleptic drug within the present invention is risperidone (Risperdal®), its manufacture and pharmacological activity is described in EP 0 196 132. Risperidone acts as an antagonist to neurotransmitters, in particular dopamine, and is used for the treatment of psychoses.

Within the present invention, the neuroleptic risperidone can be administered at a dose of 2-6 mg/day, preferably 4-5 mg. The dose for celecoxib may range from 50-1600 mg, preferably 200-600, more preferably 400 mg. Preferably, the administration occurs twice daily (in the morning and in the evening).

Various types of antidepressants can be used for the add-on use according to the present invention. Examples of antidepressants that are useful in the present invention include, but are not limited to: tricyclic antidepressants such as amitriptyline (5-(3-dimethylamino propylidene)-10,11-dihydro-*5H*-dibenzo[*a,d*]cyclohepten), amitriptyline oxide, desipramine (10,11-dihydro-5-(3-methylamino propyl)-*5H*-dibenz[*b,f*]azepin), dibenzepin (10-(2-dimethylamino ethyl)-5,11-dihydro-5-methyl-*11H*-dibenzo[*b,e*][1,4]diazepin-11-on), dosulepin (3-(6*H*-dibenzo[*b,e*]thiepin-11-yliden)-*N,N*- dimethylpropyl amine), doxepin (3-(6*H*-dibenz[*b,e*]oxepin-11-yliden)-dimethylpropyl amine), chloroimipramine, imipramine (5-(3-dimethylamino propyl)-5,11-dihydro-*5H*- dibenz[*b,f*]azepin), nortriptyline (3-(10,11-dihydro-*5H*-dibenzo[*a,d*]cyclohepten-5-yliden)-*N*-methyl-1-propane amine), mianserin (1,2,3,4,10,14b-hexahydro-2-methyl-dibenzo[*c,f*]pyrazino[1,2-α]azepin), maprotiline (N-methyl-9,10-ethanoanthracene-9(10*H*)-propane amine), trimipramine (5-[3-dimethylamino)-2-methylpropyl]-10,11-dihydro-*5H*-dibenz[*b,f*]-azepin) or viloxazine (*R*S)-2-(2-ethyoxy phenoxy methyl)-morpholine), modern antidepressants such as trazodone (2-{3-[4-(3-chlorophenyl)-1-piperazinyl]-propyl}-1,2,4-triazolo[4,3-

α]pyridine-3(2*H*)-on, nefazodone (2-{3-[4-(3-chlorophenyl)-1-piperazinyl]propyl}-5-ethyl-2,4-dihydro-4-(2-phenoxyethyl)-3*H*-1,2,4-triazol-3-on), mirtazapine ((±)-1,2,3,4,10,14b-hexahydro-2-methylpyrazino[2,1-*a*]pyrido[2,3-*c*][2]benzazepin), venlafaxine ((±)-1-2-(dimethylamino)-1-(4-methoxyphenyl)-ethyl]cyclohexanol) or reboxetine ((±)-(2*RS*)-2-[(α*SR*)-α-(2-ethoxyphenoxy)benzyl]morpholine), inhibitors of monoaminooxidases such as tranylcypromine (*trans*-2-phenyl cyclopropyl amine), brofaromine or moclobemide (4-chloro-*N*-(2-morpholinoethyl)-benzamide), selective inhibitors of serotonin-uptake such as citalopram, paroxetine, fluoxetine ((*RS*)-*N*-methyl-3-phenyl-3-[4-(trifluoromethyl)phenoxy]propyl amine, available under the tradename PROZAC®), fluvoxamine ((*E*)-5-methyoxy-4`-(trifluoromethyl)-valerophenon-*O*-(2-aminoethyl) oxime) or sertraline ((1*S*-*cis*)-(+)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-*N*-methyl-1-naphthalinamine), and vegetable antidepressants such as Hypericum (St. John`s wort).

The invention is also directed to a novel kit-of-parts that is suitable for use in the treatment of psychiatric disorders such as schizophrenia, delusional disorders, affective disorders, autism or tic disorders, comprising a first dosage form comprising a neuroleptic agent or an antidepressant and a second dosage form comprising a COX-2 inhibitor or prodrug thereof, for simultaneous, separate or sequential administration.

According to a preferred embodiment, the dosage form comprising a neuroleptic agent or an antidepressant and the second dosage form comprising a COX-2 inhibitor are administered simultaneously.

The subject pharmaceutical kit-of-parts may be administered enterally (orally) or parenterally. Parenteral administration includes subcutaneous, intramuscular, intradermal, intramammary, intravenous, and other administrative methods known in the art. Enteral administration includes solution, tablets, sustained release capsules, enteric coated capsules, and syrups. Preferably the administration of a pharmaceutical kit comprising a COX-2 inhibitor and a neuroleptic or antidepressant occurs enterally (orally), in form of tablets.

The treatment of psychiatric disorders with COX-2 inhibitors, alone or in combination with a neuroleptic or antidepressant, may occur in addition to further drug therapies. Thus, tranquilizers may be used for the treatment of agitation, anxiety or sleep disturbances. Preferably lorazepam is used, which belongs to the class of benzodiazepines.

In the following, the invention will be discussed in more detail with reference to a patient study. Other embodiments within the scope of the claims herein will be apparent to one skilled in the art from consideration of the specification or practice of the invention as disclosed herein. The results of the patient study are graphically represented in the attached figures, which will be discussed in more detail in the following.

Figure 1 shows the comparison of the PANSS score during treatment with risperidone-celecoxib or risperidone-placebo.

Figure 2 shows the comparison of the PANSS negative score during treatment with risperidone-celecoxib or risperidone-placebo.

Figure 3 shows the comparison of the PANSS global score during treatment with risperidone-celecoxib or risperidone-placebo.

Figure 4 shows the plasma levels of risperidone and 9-OH-risperidone during treatment with risperidone-celecoxib or risperidone-placebo.

Figure 5 shows the biperiden and benzodiazepine use during treatment with risperidone-celecoxib or risperidone-placebo.

The study was performed as a single-center, double-blind, placebo-controlled, randomized, parallel-groupe valuation of the combination therapy with celecoxib and risperidone versus a monotherapy with risperidone and placebo in schizophrenic patients. The study included 50 patients fulfilling the criteria for the diagnosis of schizophrenia according to DSM IV (American Psychiatric Association (1994),

Diagnostic and Statistical Manual of Mental Disorders, 1st Edition, American Psychiatric Press, Washington DC), of whom 25 belonged to the risperidone-placebo and 25 to the risperidone-celecoxib group. No significant differences were present between the two patient groups were found with regard to age, sex, duration or severity of the disease or psychopathology, risperidone dose or risperidone-plasma levels.

The patients received 2-6 mg/day of risperidone (Risperdal®), and depending on to which group they belonged, 400 mg/day of celecoxib (2x200 mg Celebrex® mornings and evenings) or placebo over 5 weeks after a brief wash-out period of earlier antipsychotic medication. During the wash-out period, a benzodiazepine preparation (mostly lorazepam) was prescribed, if necessary. Patients with agitation, anxiety, or sleeping problems were also medicated with lorazepam during the study.

The psychopathology of the patients was assessed using the positive and negative syndrome scale (PANSS) (Kay et al., Schizophr. Bull. 1987, 13:261-276).

The extrapyramidal side effects were assessed by the EPS scale (Simpson and Angus, Acta Psychiat. Scand. 1970 (Suppl.), 212). The use of biperiden was monitored as a possible indicator for side effects of the antipsychotic medication.

In order to exclude the chance that possible differences in the therapeutic effectiveness between the two groups might be due to non-compliance during the risperidone therapy or to differences in risperidone metabolism, the plasma levels of risperidone or 9-OH-risperidone were monitored during the study.

The statistics were performed according to the criterion of "last observation carried forward" (LOCF), i.e., the last PANSS scores of the patients who dropped out before the end of the study were carried forward to all subsequent observation days. For the comparison of the main efficacy parameter, the mean change in the PANSS between the two treatment groups, t-tests for independent samples were employed. With reference to the underlying hypothesis of a better outcome of the celecoxib-risperidone group, a significance of $p < 0.05$ was calculated in the one-tailed t-test

and used as the basis for the estimation of the sample size (statistical power) and for the comparison of the groups. For all other comparisons, two-tailed t-tests were used.

At the start of the study, in the risperidone-celecoxib group (average age 35.9 ± 12.8 years), the PANSS total score was 71.8 ± 17.1, the PANSS global score was 34.0 ± 8.5, the PANSS positive score was 19.0 ± 5.9 and the PANSS negative score was 18.7 ± 6.3. In the risperidone-placebo group (average age 35.5 ± 13.6 years), the PANSS total score was 75.4 ± 12.9, the PANSS global score was 37.2 ± 7.1, the PANSS positive score was 17.2 ± 4.6 and the PANSS negative score was 21.1 ± 5.5. Consequently, there was no significant difference in the PANSS total score or any of the subscales.

During the five-week therapy, a significant improvement of the PANSS total score and the subscales is observed in both groups of schizophrenic patients. The results of the PANSS total score are shown in Figure 1, of the PANSS negative score in Figure 2, of the PANSS global score in Figure 3 and of the PANSS positive score in Table 4.

Table 4
Comparison of the PANSS positive score

time	celecoxib and risperidone	placebo and risperidone	t[1]	p[2]
week 0	19.0 ± 5.9	17.2 ± 4.6	1.22	n.s.[3]
week 1	16.7 ± 5,5	16.2 ± 4.6	0.36	n.s.
week 2	14.4 ± 5.0	15 ± 4.5	0.42	n.s.
week 3	14.0 ± 4.7	14.5 ± 4.6	0.36	n.s.
week 4	12.8 ± 4.4	14.2 ± 4.4	1.16	n.s.
week 5	13.4 ± 5.6	13.3 ± 4.4	0.11	n.s.

[1] t represents the statistical random sample distribution.
[2] p represents the statistical power (probability).
[3] n.s. means no statistical significance.

In the celecoxib-risperidone group, the two-tailed t-tests between the baseline and week 5 gave the following values: PANSS total score $p < 0.0001$, PANSS global score $p < 0.0001$, PANSS positive score $p < 0.0001$, PANSS negative score $p < 0.001$. In the placebo-risperidone group, the t-tests between the baseline and week 5 gave the following values: PANSS total score $p < 0.002$, PANSS global score $p < 0.003$, PANSS positive score $p < 0.002$, PANSS negative score $p < 0.02$.

The improved effectiveness of the combination therapy with celecoxib-risperidone in comparison to risperidone monotherapy is clearly shown by the significantly lower PANSS global scores after the 2, 3, 4 and 5 weeks of treatment (Figure 3). With regard to the total and negative score, significantly lower scores were recorded after 2, 3 and 4 weeks in the celecoxib-risperidone group (Figures 1 and 2).

The mean daily dose of risperidone is shown in Table 5; no statistically significant difference was found between the two treatment groups.

Table 5
Mean risperidone dose mg/day

time	celecoxib and risperidone	placebo and risperidone	difference
week 1	4.1 ± 0.6	4.0 ± 0.8	n.s.
week 2	4.5 ± 0.6	4.4 ± 1.1	n.s.
week 3	4.8 ± 0.8	4.9 ± 1.4	n.s.
week 4	5.0 ± 1.0	4.9 ± 1.4	n.s.
week 5	4.9 ± 1.0	5.1 ± 1.5	n.s.

[1] n.s. means no statistical significance.

The differences in the plasma levels of risperidone or the metabolite 9-OH-risperidone shown in Figure 4 were also without statistical significance (the present Figure 4 differs from Figure 4 of the German patent application priority document due to a calculation error in said priority document).
Therefore, it could be excluded that the observed differences in the therapeutic effectiveness between the two groups are due to incompatibility during the

risperidone therapy or differences in risperidone metabolism. The therapeutic benefit of the combined therapy has to be attributed to the COX-2 inhibitor, celecoxib.

With respect to the extrapyramidal side effects, no statistically significant differences were found in the EPS scale. The use of biperiden is shown in Figure 5 and was calculated as cumulative weekly dose. The values were lower in the celecoxib-risperidone group, and reached statistical significance at week 2 ($p < 0.02$).

A detailed analysis of items of the PANSS-Scale which discriminate good celecoxib-responders from the placebo group revealed that therapeutic effects of celecoxib are especially found on the items "lack of contact" (item 3 of the negative subscale), "emotional isolation" (item 2 of the negative subscale), "passive-apathic isolation" (item 4 of the negative subscale), "social withdrawal" (item 16 of the general psychopathology subscale), "depression" (item 6 of the general psychopathology subscale) and "motor retardation" (item 6 of the general psychopathology subscale). Furthermore, a factor analysis showed that especially items which can subsumed under the label "agitation" show a good therapeutic response to celecoxib, but not to placebo. All those items reflect psychopathological symptoms which are typically found in depressive states. Therefore this detailed analysis points to a therapeutic efficiency in depressive states.

Moreover, "passive-apathic isolation", "motor retardation", "social withdrawal", or "lack of contact" are -often more severe expressed than in depressive states - also core-symptoms of childhood autism.

The combination of celecoxib and risperidone according to the present invention thus shows improved results compared to the monopreparation risperidone with regard to effectiveness in the treatment of schizophrenia. Furthermore, it was observed that the beneficial effects of the add-on therapy occurred faster in patients with a recent onset of the disorder and that the celecoxib therapy was useful in the treatment of depressive states.

Patent Claims

1. Use of a COX-2 inhibitor in the preparation of a medicament for the treatment of psychiatric disorders.

2. Use according to Claim 1 for the treatment of schizophrenia, delusional disorders, affective disorders, autism and tic disorders.

3. Use according to Claim 1 or 2 for the treatment of chronic schizophrenic psychoses, schizoaffective psychoses, temporary acute psychotic disorders, depressive episodes, recurring depressive episodes, manic episodes and bipolar affective disorders.

4. Use according to anyone of Claims 1 to 3, characterized in that the COX-2 inhibitor is selected from celecoxib, rofecoxib, meloxicam, piroxicam, deracoxib, parecoxib, valdecoxib, etoricoxib, a chromene derivative, a chroman derivative, N-(2-cyclohexyloxynitrophenyl)methane sulfonamide, COX189, ABT963 or JTE-522, pharmaceutically acceptable salts, prodrugs or mixtures thereof.

5. Use according to Claim 4, characterized in that celecoxib or a pharmaceutically acceptable salt thereof is used as COX-2 inhibitor.

6. Use according to Claim 5, characterized in that celecoxib or a pharmaceutically acceptable salt thereof is administered in an amount of 50-1600 mg per day, preferably 200 to 600 mg, most preferably 400 mg.

7. Use according to anyone of the preceding Claims, characterized in that the medicament is administered orally.

8. Use of a COX-2 inhibitor in combination with a neuroleptic drug or an antidepressant in the preparation of a medicament for the treatment of psychiatric disorders.

9. Use according to Claim 8 for the treatment of schizophrenia, delusional disorders, affective disorders, autism and tic disorders.

10. Use according to Claim 8 or 9 for the treatment of chronic schizophrenic psychoses, schizoaffective psychoses, temporary acute psychotic disorders, depressive episodes, recurring depressive episodes, manic episodes and bipolar affective disorders.

11. Use according to anyone of Claims 8 to 10, characterized in that the COX-2 inhibitor is selected from celecoxib, rofecoxib, meloxicam, piroxicam, deracoxib, parecoxib, valdecoxib, etoricoxib, a chromene derivative, a chroman derivative, N-(2-cyclohexyloxynitrophenyl)methane sulfonamide, COX189, ABT963 or JTE-522, pharmaceutically acceptable salts, prodrugs or mixtures thereof.

12. Use according to Claim 11, characterized in that celecoxib or a pharmaceutically acceptable salt thereof is used as COX-2 inhibitor.

13. Use according to anyone of Claims 8 to 12, characterized in that the neuroleptic is selected from clozapine, olanzapine, ziprasidone, risperidone, aripiprazole, quetiapine, quetiapine fumarate, sertindole, amisulpride, haloperidol, haloperidol decanoate, haloperidol lactate, chlorpromazine, fluphenazine, fluphenazine decanoate, fluphenazine enanthate, fluphenazine hydrochloride, thiothixene, thiothixene hydrochloride, trifluoperazine, perphenazine, amitriptyline, thioridazine, mesoridazine, molindone, molindone hydrochloride, loxapine, loxapine hydrochloride, loxapine succinate, pimozide, flupenthixol, promazine, triflupromazine, chlorprothixene, droperidol, actophenazine, prochlorperazine, methotrimeprazine, pipotiazine, ziprasidone, hoperidone, zuclopenthixol, and mixtures thereof.

14. Use according to anyone of Claims 8 to 12, characterized in that the antidepressant is selected from amitriptyline, amitriptyline oxide, desipramine, dibenzepin, dosulepin, doxepin, chloroimipramine, imipramine, nortriptyline, mianserin, maprotiline, trimipramine, viloxazine, trazodone, nefazodone, mirtazapine, venlafaxine, reboxetine, tranylcypromine, brofaromine, moclobemide, citalopram, paroxetine, fluoxetine, fluvoxamine, sertraline, Hypericum (St. John's Wort), and mixtures thereof.

15. Use according to Claim 13, characterized in that risperidone or aripiprazole is used as a neuroleptic.

16. Use according to Claim 12 and 15, characterized in that celecoxib or a pharmaceutically acceptable salt thereof and risperidone are administered in an amount of 50-1600 mg, preferably 200-600 mg, and 2-6 mg, respectively.

17. Use according to Claim 16, characterized in that celecoxib or a pharmaceutically acceptable salt thereof and risperidone are administered in an amount of 400 mg and 4-5 mg, respectively.

18. Use according to anyone of Claims 8 to 17, characterized in that the medicament is administered orally.

19. Use according to anyone of the preceding Claims, characterized in that a tranquilizer, preferably lorazepam, is administered additionally.

20. Kit-of-parts suitable for use in the treatment of psychiatric disorders, comprising a first dosage form comprising a neuroleptic drug or an antidepressant and a second dosage form comprising a COX-2 inhibitor or prodrug thereof, for simultaneous, separate or sequential administration.

21. Kit-of-parts according to Claim 20, characterized in that the neuroleptic is selected from clozapine, olanzapine, ziprasidone, risperidone, quetiapine,

quetiapine fumarate, sertindole, amisulpride, haloperidol, haloperidol decanoate, haloperidol lactate, chlorpromazine, fluphenazine, fluphenazine decanoate, fluphenazine enanthate, fluphenazine hydrochloride, thiothixene, thiothixene hydrochloride, trifluoperazine, perphenazine, amitriptyline, thioridazine, mesoridazine, molindone, molindone hydrochloride, loxapine, loxapine hydrochloride, loxapine succinate, pimozide, flupenthixol, promazine, triflupromazine, chlorprothixene, droperidol, actophenazine, prochlorperazine, methotrimeprazine, pipotiazine, ziprasidone, hoperidone, zuclopenthixol, and mixtures thereof.

22. Kit-of-parts according to Claim 20, characterized in that the antidepressant is selected from amitriptyline, amitriptyline oxide, desipramine, dibenzepin, dosulepin, doxepin, chloroimipramine, imipramine, nortriptyline, mianserin, maprotiline, trimipramine, viloxazine, trazodone, nefazodone, mirtazapine, venlafaxine, reboxetine, tranylcypromine, brofaromine, moclobemide, citalopram, paroxetine, fluoxetine, fluvoxamine, sertraline, Hypericum (St. John`s Wort), and mixtures thereof.

23. Kit-of-parts according to anyone of Claims 20 to 22, characterized in that the COX-2 inhibitor is selected from celecoxib, rofecoxib, meloxicam, piroxicam, deracoxib, parecoxib, valdecoxib, etoricoxib, a chromene derivative, a chroman derivative, N-(2-cyclohexyloxynitrophenyl)methane sulfonamide, COX189, ABT963 or JTE-522, pharmaceutically acceptable salts, prodrugs or mixtures thereof.

24. Kit-of-parts according to anyone of Claims 20, 21 or 23, characterized by comprising celecoxib or a pharmaceutically acceptable salt thereof as COX-2 inhibitor and risperidone as neuroleptic drug.

25. Kit-of-parts according to Claim 24, characterized by comprising celecoxib or a pharmaceutically acceptable salt thereof and risperidone in an amount of 50-1600 mg and 2-6 mg, respectively.

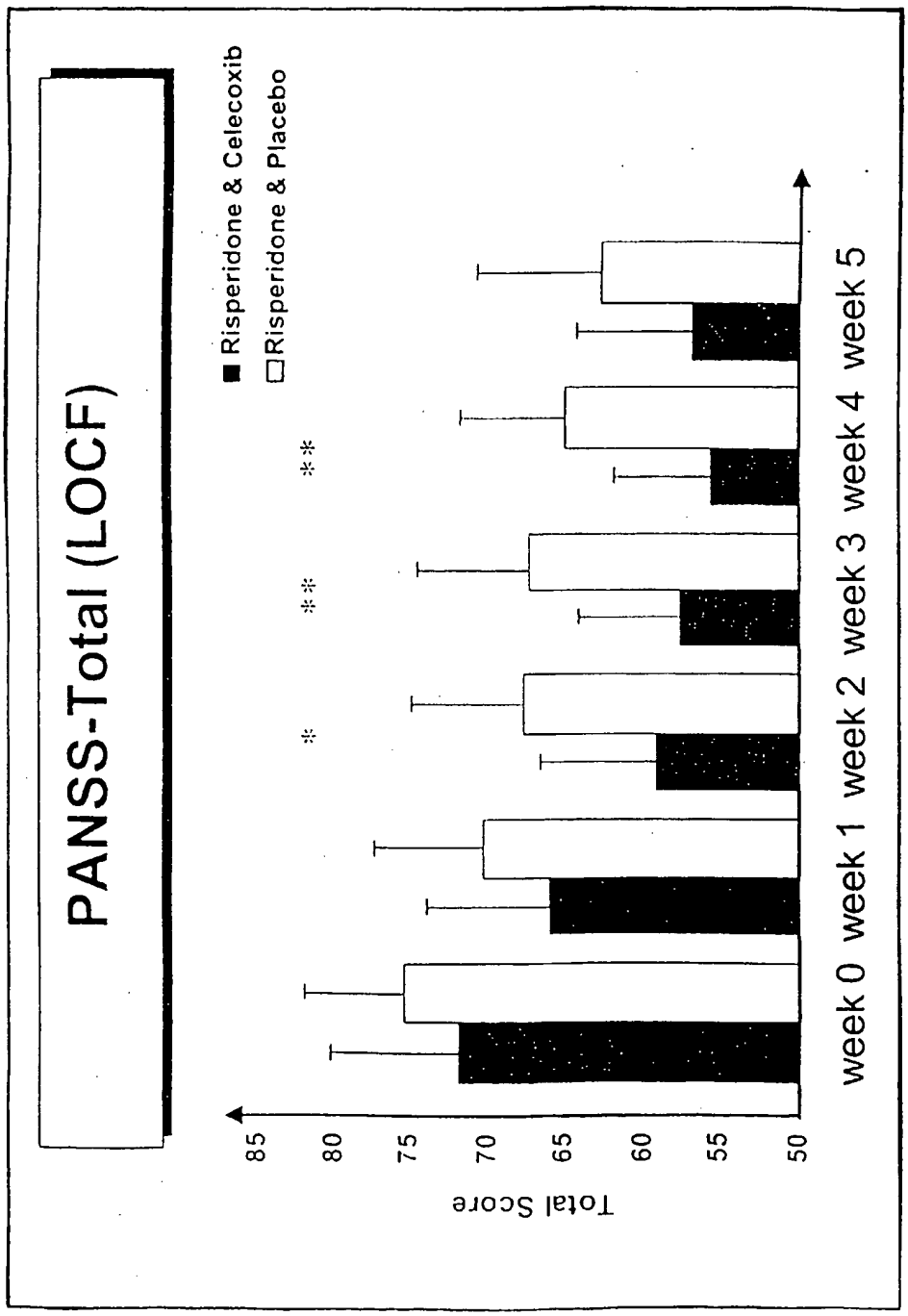


Figure 1: Comparison of the Panss total score during the treatment course of risperidone and celecoxib or risperidone and placebo

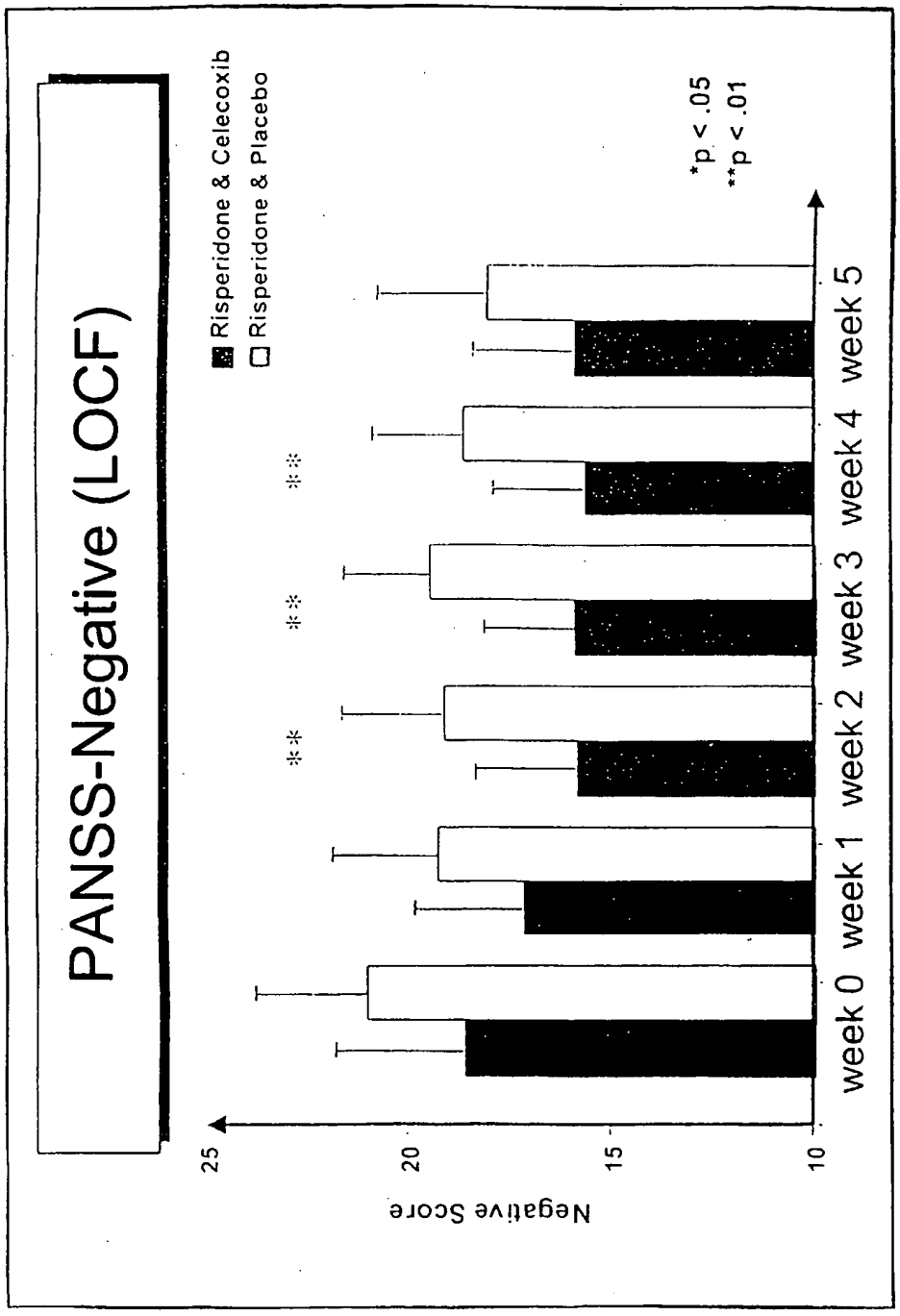


Figure 2: Comparison of the Panss negative score during the treatment course of risperidone and celecoxib or risperidone and placebo

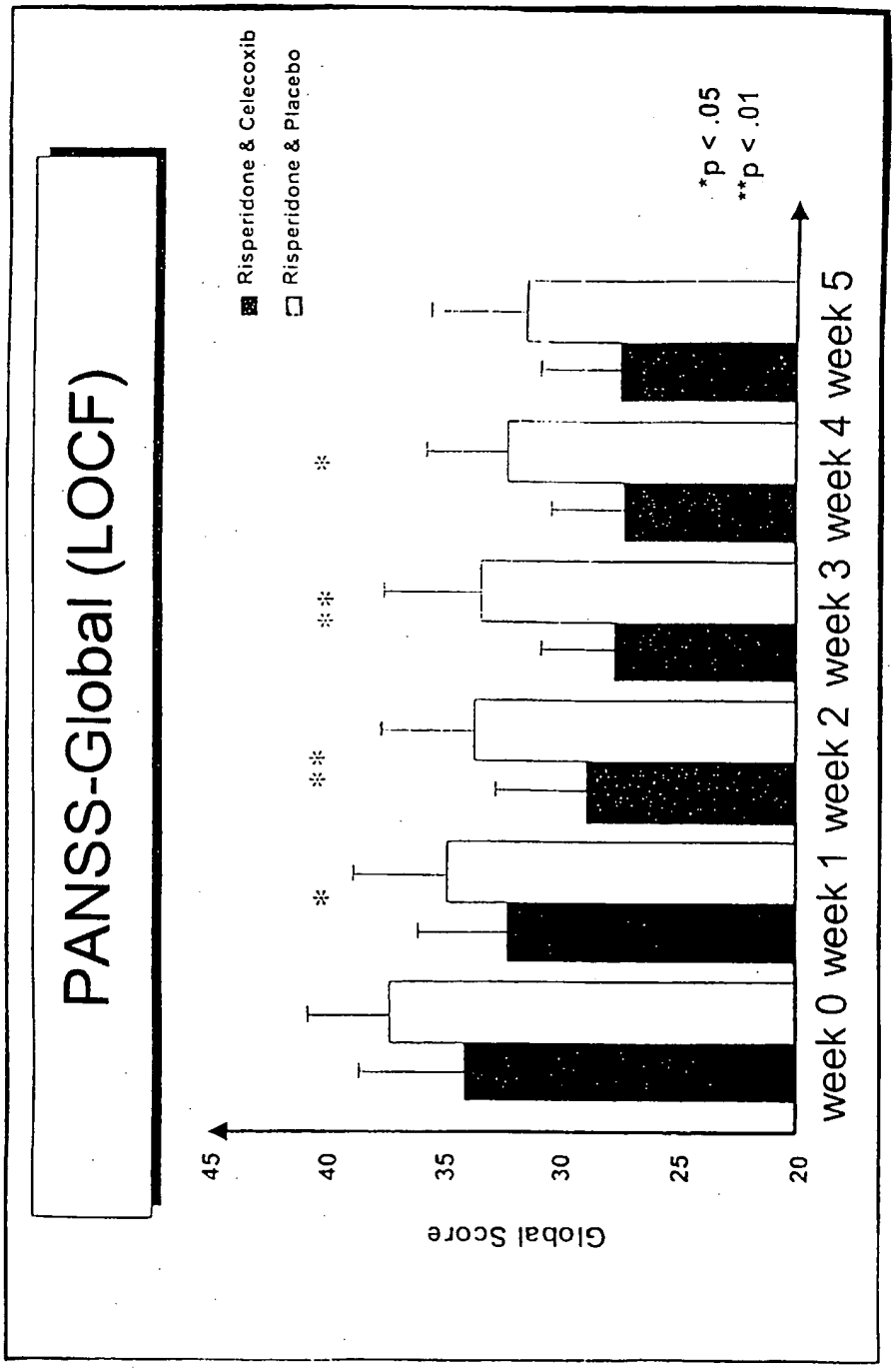


Figure 3: Comparison of the Panss global score during the treatment course of risperidone and celecoxib or risperidone and placebo

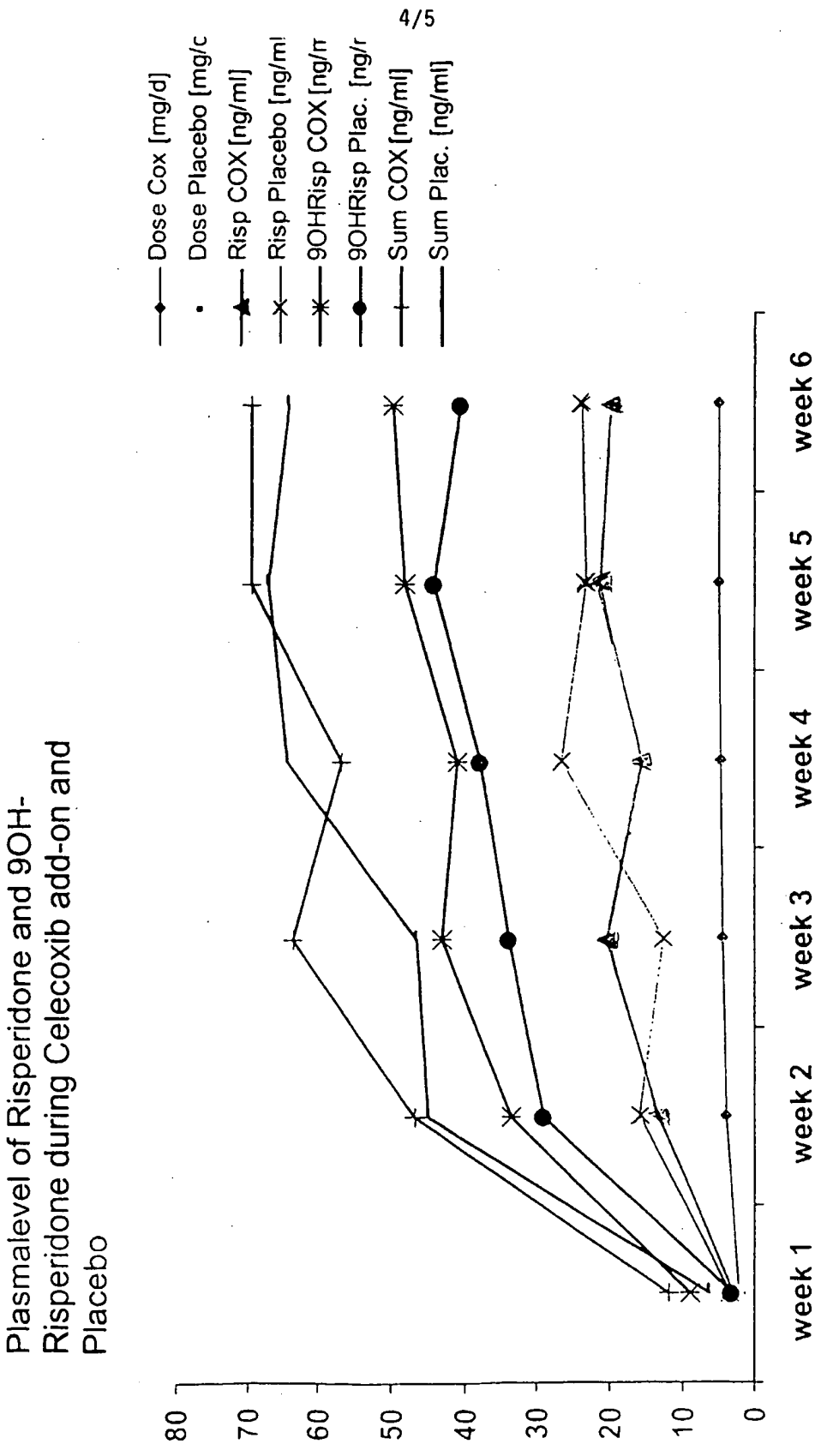


Figure 4: Plasma levels of Risperidone and 9OH-Risperidone during Celecoxib add-on and Placebo

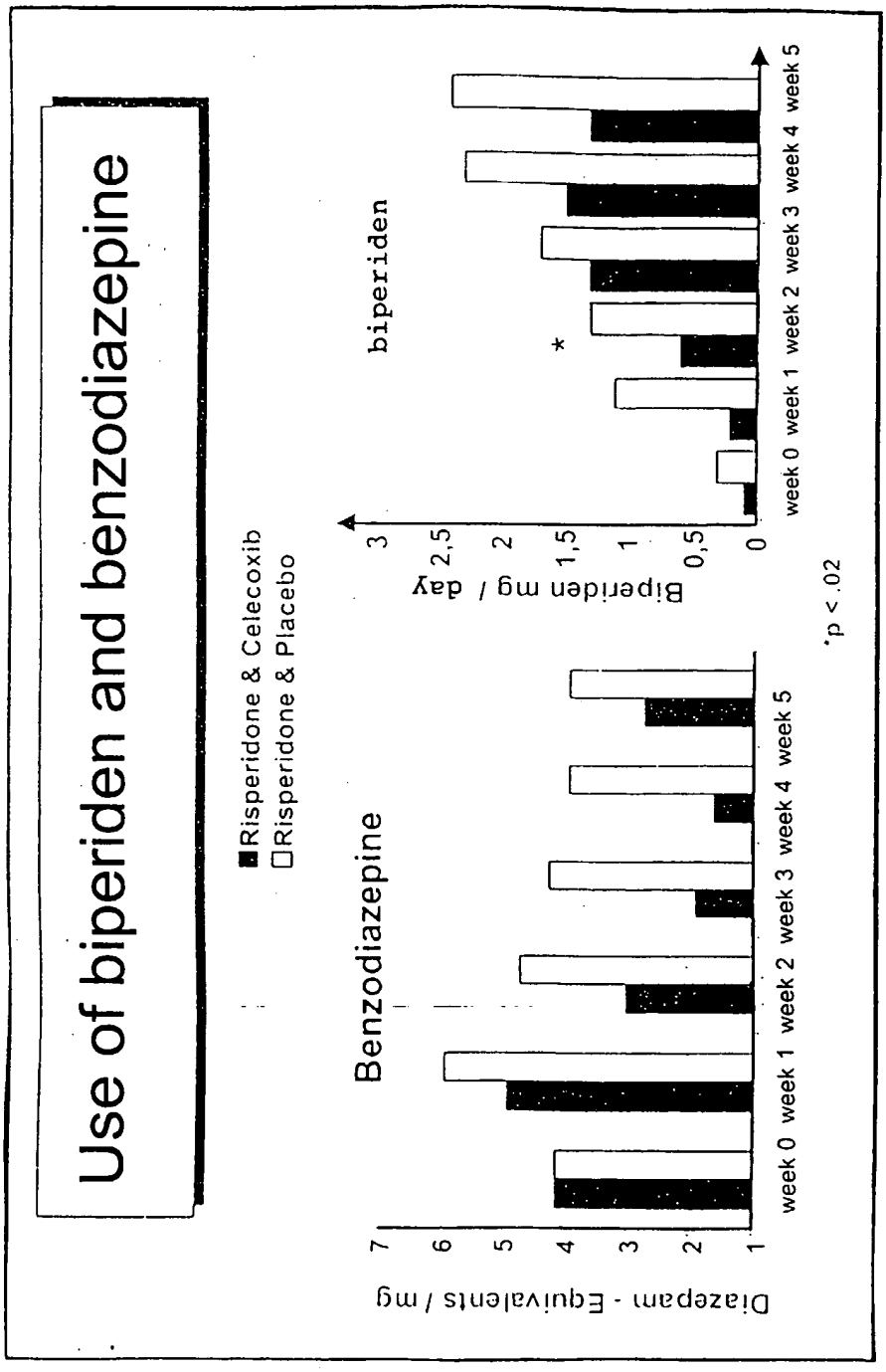


Figure 5: Use of biperiden and benzodiazepines during the Treatment with risperidone-celecoxib or risperidone-placebo